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EDITORIAL

Medicines information: dwindling support in the age of information overload

Felicity Prior
Director, Hunter Drug Information Service, Calvary Mater Newcastle, Waratah, New South Wales

Conjoint senior lecturer, School of Biomedical Sciences and Pharmacy, Faculty of Health and Medicine, University of Newcastle, New South Wales

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Patients and their treatments are becoming increasingly complex. Managing these patients requires knowledge and understanding of the medicines used in treatment. Medicines information is therefore an important component of the quality use of medicines.[1] It informs safe and effective practice, optimising outcomes for the individual and the broader population. However, access to specialised medicines information services has reduced in parts of Australia.

There is a lot of medicines information available and it comes from many different sources.[2] However, not all sources are reliable and an appraisal of their currency and relevance is required to ensure the information is of high quality. Health professionals have variable access to these resources and many require paid subscriptions. While the list of required resources to be held in community pharmacies is mandated by the Pharmacy Board of Australia, there is no similar list for medical practices, where 406,000 patient interactions occur each day.[3] Even with access to specific resources, the challenge for health professionals often lies in the time and expertise required to locate, analyse and use medicines information for clinical decision making within a busy practice.

There is no one perfect source of medicines information. Limitations exist with every resource, regardless of currency and provenance. For example, the readily available product information approved by the Therapeutic Goods Administration, which many health professionals rely on for decision support, only provides data for registered indications. It is not useful when considering off-label use. There may be no information about prescribing for children. Obstetric information is often limited to animal data or pregnancy categorisations which can result in misinterpretation of risk.[4] Newer drugs will have an incomplete safety profile due to the limited number of patients in premarketing clinical trials, and the product information for older drugs may be out of date.

The challenge lies not only in the identification and analysis of accurate, current, unbiased and evidence-based information, but the formulation of a clear and practical recommendation for each individual at a particular point in time. Complex clinical dilemmas are often not resolved by merely locating information unless there is accompanying expert interpretation. Electronic decision-support tools do not equate to specialist advice. This is where specialised support services can assist.

There are a number of specialist support services currently available in Australia. They provide a range of medicines information to consumers, health professionals or both. These services are funded independently of each other, by a variety of organisations at a local, state or national level.

Such support services include:

- alcohol and drug information services
- Medicines Line (consumers only)
- Mothersafe
- NSW Cannabis Medicines Advisory Service
- Poisons Information Centres.

Medicines information services, operated by experienced and specialist-trained pharmacists, are located within some major tertiary hospitals. Despite primary care being the source of most prescribing, only some services accept calls from GPs or the general public. The scope of each service is dependent on funding and each service is unique.

While difficult to quantitate the clinical and economic impact, users of these medicines information services report a high level of satisfaction and positive impact on patient care.[5-7] A large proportion of users rely on advice before continuing management, with the majority of advice being accepted and acted upon. A model used to determine potential cost savings or 'avoidance' of costs associated with advice estimated annual potential savings of up to US$2 million.[8]

Without warning or external consultation, the NSW Medicines Information Centre closed in April 2018. Community-based health professionals across New South Wales had relied on the expertise provided by the team of experienced pharmacists who had operated this service since 1980. There were on average 1200 enquiries per year. The health professionals who used this service were left without a satisfactory alternative.

Unfortunately, this is not the first time a medicines information service has been closed. Similar state-based services in Tasmania, Victoria and Western Australia ceased operation or limited their scope, and services in South Australia have been restructured. NPS MedicineWise funded the Therapeutic Advice

and Information Service which was delivered by a consortium of six established medicines information services. From 2000–2010 this service provided responses to over 6000 community-based health professionals a year across Australia, with most enquiries from GPs and community pharmacists.[9] The service capitalised on the shared use of existing infrastructure, expertise, training and resources at individual sites. NPS discontinued funding after concluding that it was not sustainable.[9]

In the absence of these specialised services, a quarter of hospital-based users say they would instead use the internet.[7] Other alternatives of varying quality include books, or resources provided by pharmaceutical companies. People may also seek complex medicines information from another pharmacist or professional colleague. In addition, only half of clinicians' clinical questions are pursued, due to a number of barriers including a lack of time.[10] Limited access to specialised services could further increase this number, potentially impacting adversely on patient care. In addition, there will be fewer opportunities for trainee medicines information specialists to gain practical experience. The loss of opportunities for pharmacists to obtain specialised training in medicines information is an important consideration. It could conceivably reduce the quality of information provided.

While access to information may be easier and faster than ever before, there is still a need for competent evaluation of data and individualised management plans. For new drugs the need for information is likely to increase as more drugs will be fast-tracked onto the Australian market.

Despite these needs, funding restrictions are affecting access to medicines information services especially for community health professionals who provide the majority of care for Australians. The need for timely, accurate, current, unbiased, clinically relevant, evidence-based therapeutic advice will continue, but who is willing to pay for this? <

Conflict of interest: none declared

REFERENCES

1. Smith A. Quality use of medicines – are we nearly there yet? Aust Prescr 2012;35:174-5. https://doi.org/10.18773/austprescr.2012.077
2. Day RO, Snowden L. Where to find information about drugs. Aust Prescr 2016;39:88-95. https://doi.org/10.18773/austprescr.2016.023
3. Australian Institute of Health and Welfare. Australia's health 2018. Canberra: AIHW; 2018. https://www.aihw.gov.au/reports/australias-health/australias-health-2018/contents/table-of-contents [cited 2019 Nov 1]
4. Kennedy D. Classifying drugs in pregnancy. Aust Prescr 2014;37:38-40. https://doi.org/10.18773/austprescr.2014.018
5. Innes AJ, Bramley DM, Wills S. The impact of UK Medicines Information services on patient care, clinical outcomes and medicines safety: an evaluation of healthcare professionals' opinions. Eur J Hosp Pharm Sci Pract 2014;21:222-8. https://doi.org/10.1136/ejhpharm-2014-000462
6. Bramley D, Mohandas C, Soor S, Erskine D, Oborne A. Does a medicines information service have a positive impact on patient care? Pharm J 2009;282:139-40.
7. Hands D, Stephens M, Brown D. A systematic review of the clinical and economic impact of drug information services on patient outcome. Pharm World Sci 2002;24:132-8. https://doi.org/10.1023/A:1019573118419
8. Kinky DE, Erush SC, Laskin MS, Gibson GA. Economic impact of a drug information service. Ann Pharmacother 1999;33:11-6. https://doi.org/10.1345/aph.18218
9. McGuire T, Patounas M. Goodbye TAIS and thanks for all the information! Aust Prescr 2010;33:147-9. https://doi.org/10.18773/austprescr.2010.069
10. Del Fiol G, Workman TE, Gorman PN. Clinical questions raised by clinicians at the point of care: a systematic review. JAMA Intern Med 2014;174:710-8. https://doi.org/10.1001/jamainternmed.2014.368

LETTERS

Letters to the Editor

When should treatment be started for hypertension?

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The article by Emily Atkins and Vlado Perkovic[1] provides a welcome review of contemporary issues regarding blood pressure and vascular risk. Understanding blood pressure and its relationship to premature morbidity and mortality, and the use of effective interventions, has been a major success of the last 100 years. Yet, areas of uncertainty remain.

In contrast to previous definitions, the new, lower definition of hypertension adopted in recent US guidelines[2] is based on the level of blood pressure where there is increased cardiovascular risk (observational data), rather than where treatment (interventional data) has demonstrated a net benefit. The recent article[1] suggests that antihypertensive treatment may be worthwhile at a systolic blood pressure of less than 140 mmHg. However, there is little direct evidence to support this in patients without established vascular disease. The SPRINT trial[3] is not informative for treatment thresholds, as 90% of the patients were established on therapy before enrolment. In contrast, the HOPE 3 trial[4] demonstrated that baseline blood pressure was a significant determinant of risk reduction in intermediate-risk individuals. Those with higher blood pressure (systolic >143.5 mmHg) benefited from therapy, while those with lower blood pressure did not. A well-designed meta-analysis (incorporating the PICO elements of patient population, intervention, comparator and outcome) also suggests a treatment benefit with a threshold of 140 mmHg systolic.[5]

A careful approach is also needed in people with elevated blood pressure, who could, by virtue of age and sex, be considered low risk. Early clinical trials,[6] where blood pressures were markedly elevated, had very high event rates, and very low numbers needed to treat (NNT=2) to prevent one event over 12 months. It is important to understand, particularly for younger doctors who may have limited personal experience with managing accelerated or malignant hypertension,[7,8] that hypertension can be a disease, as well as a risk factor.

Rather than the unnecessarily polarising view that a cardiovascular risk-based approach is best for determining when to start antihypertensive therapy, a more nuanced approach is helpful. Decisions on initiating antihypertensives should be based on both blood pressure and risk, as has been advocated in Australian blood pressure guidelines for some years.[9]

Genevieve Gabb
Senior staff specialist, Royal Adelaide Hospital, SA

Professor Leonard Arnolda
Clinical Director, Illawarra Health and Medical Research Institute, University of Wollongong, NSW

Dr Genevieve Gabb is a member of the Advisory Editorial Panel of Australian Prescriber, *as representative of the High Blood Pressure Research Council of Australia.*

REFERENCES

1. Atkins ER, Perkovic V. Blood pressure: at what level is treatment worthwhile? Aust Prescr 2019;42:127-30. https://doi.org/10.18773/austprescr.2019.038
2. Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines. J Am Coll Cardiol 2018;71:e127-248. https://doi.org/10.1016/j.jacc.2017.11.006
3. Wright JT Jr, Williamson JD, Whelton PK, Snyder JK, Sink KM, Rocco MV, et al.; SPRINT Research Group. A randomized trial of intensive versus standard blood-pressure control. N Engl J Med 2015;373:2103-16. https://doi.org/10.1056/NEJMoa1511939
4. Lonn EM, Bosch J, López-Jaramillo P, Zhu J, Liu L, Pais P, et al.; HOPE-3 Investigators. Blood-pressure lowering in intermediate-risk persons without cardiovascular disease. N Engl J Med 2016;374:2009-20. https://doi.org/10.1056/NEJMoa1600175
5. Brunström M, Carlberg B. Association of blood pressure lowering with mortality and cardiovascular disease across blood pressure levels: a systematic review and meta-analysis. JAMA Intern Med 2018;178:28-36. https://doi.org/10.1001/jamainternmed.2017.6015
6. Veterans Administration Cooperative Study Group on Antihypertensive Agents. Effects of treatment on morbidity in hypertension: results in patients with diastolic blood pressures averaging 115 through 129 mm Hg. JAMA 1967;202:1028-34. https://doi.org/10.1001/jama.1967.03130240070013
7. Keith NM, Wagener HP, Kernohan JW. The syndrome of malignant hypertension. Arch Intern Med (Chic) 1928;41:141-88. https://doi.org/10.1001/archinte.1928.00130140003001
8. Kincaid-Smith P, McMICHAEL J, Murphy EA. The clinical course and pathology of hypertension with papilloedema (malignant hypertension). Q J Med 1958;27:117-53.
9. Gabb GM, Mangoni AA, Anderson CS, Cowley D, Dowden JS, Golledge J, et al. Guideline for the diagnosis and management of hypertension in adults - 2016. Med J Aust 2016;205:85-9. https://doi.org/10.5694/mja16.00526

The recent article[1] predominantly discusses blood pressure treatment targets, not thresholds. The recommendations are based largely on the SPRINT study[2] and the recent US guidelines.[3] The authors suggest, quoting one reference, that blood pressure measurement in SPRINT (automated office blood pressure) equates to usual clinic blood pressure

The Editorial Executive Committee welcomes letters, which should be less than 250 words. Before a decision to publish is made, letters which refer to a published article may be sent to the author for a response. Any letter may be sent to an expert for comment. When letters are published, they are usually accompanied in the same issue by any responses or comments. The Committee screens out discourteous, inaccurate or libellous statements. The letters are sub-edited before publication. Authors are required to declare any conflicts of interest. The Committee's decision on publication is final.

measurement. However, the majority opinion is that systolic blood pressure measured by automated office blood pressure is 10–20 mmHg lower than usual clinic blood pressure,[4,5] which has been used in all the clinical trials that provide the evidence base for the treatment of hypertension. In SPRINT, achieving systolic blood pressure less than 120 mmHg was also associated with serious treatment-related adverse events. SPRINT is therefore not a suitable study on which to base major treatment recommendations.

In contrast, the recent European hypertension guidelines[5] have provided a well-argued case that treatment to lower blood pressure with both lifestyle change and drug therapy is of benefit if the 'clinic' systolic blood pressure is more than 140 mmHg, across the range of blood pressures, cardiovascular risk, comorbidity, sex, ethnicity and age up to 80 years. This was based on available evidence including the SPRINT trial. The European guidelines also demonstrate the lack of evidence for initiating treatment if systolic blood pressure is 130–140 mmHg, except possibly for those at very high cardiovascular risk and with established cardiovascular disease.

Target systolic blood pressure should initially be less than 140 mmHg and, if tolerated, less than 130 mmHg but not less than 120 mmHg. In my opinion the European recommendations are more broadly applicable to the management of hypertension in Australia than the recommendations given in the article.

Emeritus Professor Lindon Wing
Flinders University, Adelaide, SA

Lindon Wing is Chair of the Management Committee of the Second Australian National Blood Pressure Study.

REFERENCES

1. Atkins ER, Perkovic V. Blood pressure: at what level is treatment worthwhile? Aust Prescr 2019;42:127-30. https://doi.org/10.18773/austprescr.2019.038
2. Wright JT Jr, Williamson JD, Whelton PK, Snyder JK, Sink KM, Rocco MV, et al.; SPRINT Research Group. A randomized trial of intensive versus standard blood-pressure control. N Engl J Med 2015;373:2103-16. https://doi.org/10.1056/NEJMoa1511939
3. Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines. J Am Coll Cardiol 2018;71:e127-248. https://doi.org/10.1016/j.jacc.2017.11.006
4. Myers MG, Godwin M, Dawes M, Kiss A, Tobe SW, Kaczorowski J. Measurement of blood pressure in the office: recognizing the problem and proposing the solution. Hypertension 2010;55:195-200. https://doi.org/10.1161/HYPERTENSIONAHA.109.141879
5. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, et al; Authors/Task Force Members. 2018 ESC/ESH guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension. J Hypertens 2018;36:1953-2041. https://doi.org/10.1097/HJH.0000000000001940

Emily Atkins and Vlado Perkovic, the authors of the article, comment:

We thank the letter writers for their responses and welcome the discussion.

A key issue is their suggested separation of treatment thresholds from treatment targets. We disagree with this distinction, and believe that blood pressure targets and thresholds should be considered consistently, once a decision to intervene is reached. We agree that blood pressure treatment is worthwhile in hypertensive urgencies or emergencies, and blood pressure should be considered separately in this specific context.

We strongly believe SPRINT should guide blood pressure treatment approaches. The small increase in adverse events was clearly outweighed by a substantive reduction in cardiovascular events *and* all-cause mortality. It is criticised for the rigorous approach to blood pressure measurement, but we believe this careful measurement is a strength and would advocate for its recommendation and incorporation in guidelines, as has happened in US and Canadian guidelines.[1,2] We believe this is a small ask given patients are committed to potentially lifelong therapy.

Genevieve Gabb and Leonard Arnolda highlighted a meta-analysis. However, this did not exclude trials of dual inhibition of the renin–angiotensin–aldosterone system, which has minimal effects on blood pressure, substantial toxicity, and is contraindicated in guidelines. They highlight the HOPE 3 heterogeneity by baseline blood pressure, but we note the blood pressure reduction achieved in this trial was only 3 mmHg, limiting power. The 95% confidence intervals for the treatment estimate are still consistent with a 19% risk reduction even for participants in the lowest blood pressure tertile. We agree additional data would be helpful.

We believe targeting systolic blood pressure less than 120 mmHg in high-risk people will ensure maximal cardiovascular protection if it is tolerated and appropriate for the individual patient.

REFERENCES

1. Muntner P, Shimbo D, Carey RM, Charleston JB, Gaillard T, Misra S, et al. Measurement of blood pressure in humans: a scientific statement from the American Heart Association. Hypertension 2019;73:e35-66. https://doi.org/10.1161/HYP.0000000000000087
2. Nerenberg KA, Zarnke KB, Leung AA, Dasgupta K, Butalia S, McBrien K, et al.; Hypertension Canada. Hypertension Canada's 2018 guidelines for diagnosis, risk assessment, prevention, and treatment of hypertension in adults and children. Can J Cardiol 2018;34:506-25. https://doi.org/10.1016/j.cjca.2018.02.022

ARTICLE

Psychoactive drugs and driving

Vanita Parekh
Director, Clinical Forensic Medical Services, Canberra Hospital, ACT

Associate professor, Australian National University

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driving under the influence, psychotropic drugs, traffic accidents

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SUMMARY

Any drug or substance with effects on the central nervous system can impair the ability to drive safely.

When prescribing, consider the effects of each drug on driving as well as the use of other substances. Advise the patient of the risks.

Opioids, benzodiazepines, anticonvulsants, antipsychotics and sedating antidepressants increase the risk of crashing. Erratic use of sedatives causes a higher level of impairment than stable regimens.

Patients who have complex medical conditions and take multiple drugs should undergo a fitness-to-drive assessment.

Introduction

Any psychoactive substance acting on the central nervous system can impair driving skills. These substances may be prescribed drugs, alcohol or substances of misuse. Alcohol, cannabis, opioids, stimulants and sedating drugs, such as benzodiazepines, are the substances of greatest concern in road safety.

While alcohol use has been declining, there has been an increase in the detection of other impairing substances in drivers. Misuse of prescription drugs is a concern, especially in relation to deaths from opioid use. Drugs affecting the ability to drive safely that have an increasing profile in motor vehicle collisions include pregabalin and gabapentin. Gabapentinoids may be being misused for their euphoric and dissociative effects.[1,2]

In Victoria, prescription drugs were involved in approximately 21% of fatal road collisions from 2007–2013. The prevalence varies in other states and territories depending on jurisdictional practice and data collection.[3]

The tasks of driving

Driving is a complex task that places demands on vision, rapid decision making, planning, tracking, vigilance, reaction time, coordination and gross motor activity. Most importantly, driving requires the ability to divide attention between several competing demands on cognitive skill. Any of these functions can be adversely affected by psychoactive substances either alone or in combination.

Alcohol is the most thoroughly understood drug with regard to driving ability. It is often used as a benchmark for drug effects, even though it has very little similarity with the pharmacokinetics and dynamics of other drugs.

Random testing

At present, random roadside alcohol and drug testing occurs to a variable extent throughout Australia. Alcohol testing involves a screening breath analysis followed by confirmatory testing with highly sensitive and specific instruments. When a confirmatory sample cannot be obtained, blood testing may be required.

Random roadside samples of saliva are tested for three substances:

- delta-9-tetrahydrocannabinol (cannabis)
- methamphetamine (commonly known as ice or speed)
- 3,4-methylenedioxymethylamphetamine (MDMA, commonly known as ecstasy).

These drugs were originally selected to avoid legal defences based on prescribed medicines. Screening is done at the roadside with an oral wipe. If the result is positive, an oral fluid sample is taken and sent for confirmatory testing. Cut-off concentrations for driving offences are set according to the Australian Standard (AS/NZS 4760-2019) or local policies.

Mandatory testing

Mandatory testing is required following a motor vehicle collision. Blood, and in some jurisdictions, urine, is collected. Samples are screened for commonly used substances including alcohol. If there is a positive indication, confirmatory tests are carried out. Observation of impaired driving behaviour in conjunction with blood sampling is generally required to prove the offence of driving under the influence, particularly for prescription drugs. Drug concentrations on their own do not predict individual driving ability due to the user developing tolerance to the drug.

Medical conditions

The underlying medical condition for which a drug is prescribed may also have potential effects on driving ability. It is common in drivers with chronic conditions for there to be multiple effects on driving ability due to the illnesses and the drugs used to treat them.[4] For further information on medical conditions and driving, refer to Austroads: Assessing Fitness to Drive.[5] Many of the drug information databases used by doctors and pharmacists provide advice on the effects of drugs on driving. The more stringent requirements for commercial drivers are given in the Austroad standards.

Depression

Depression impairs driving skills such as cognitive abilities and concentration. It slows reaction times and can therefore increase the risk of a crash.[6] Sedating antidepressant drugs, especially the tricyclic antidepressants, are likely to contribute to the increased risk. This risk decreases after six weeks, but not necessarily to the normal baseline level of control.[7]

Epilepsy

Most studies report an increased crash risk in people with epilepsy.[8] Anticonvulsants frequently have adverse effects, such as fatigue, incoordination and dizziness, with the potential to impair driving ability. Starting or changing treatment including withdrawal of anticonvulsants alters the risk of seizures. Discussion and recommendation with regard to not driving and driving-free periods should be provided to the patients preferably in a written form with clear documentation in the prescriber's and dispenser's records. Providing a copy of the Austroad standards relevant to epilepsy is a useful adjunct to management.

Alcohol

Alcohol is the most common substance involved in road traffic collisions and deaths. Like most sedating drugs, alcohol impairs the ability to drive by increasing reaction time and decreasing concentration, coordination and tracking. It also increases risk-taking behaviour as drivers overestimate their skills. Alcohol is the only substance for which there is a generally accepted relationship between blood concentrations and the risk of crashing.

Alcohol interlocks are breath analysis devices installed in a vehicle. They require the driver to provide a breath sample before driving and at random times during a drive. Interlocks are useful for ensuring chronic alcohol users do not drive while intoxicated but they are expensive. In most jurisdictions their use cannot be made a condition for holding a driving licence unless there is a court order.

Sedatives

For sedating drugs, particularly benzodiazepines and opioids, the risk of having a motor vehicle collision is increased in the first four weeks after starting treatment and especially when combined with alcohol. Anticonvulsants, antidepressants and antipsychotics can also have sedative effects with the potential to affect driving ability. The prescriber and pharmacist must warn patients of these effects.[9]

An increased dose of any sedating substance will increase crash risk as will the absence of tolerance. There are other factors that affect the ability to drive safely such as the initiation period, time to steady state and effect, pre-existing medical conditions, driver experience and combinations with other substances.

Stabilisation on sedative drugs will generally take 6–8 weeks. In certain circumstances tolerance may develop, decreasing the crash risk from sedating drugs taken on a regular dosing schedule as long as other substances or alcohol are not used. The intermittent and erratic use of sedating substances can lead to unsafe driving.

Patients on a stable maintenance dose of opioid replacement therapy, such as methadone, will develop a tolerance to its sedating effects. They are usually safe to drive providing the opioid replacement therapy is taken as directed and no psychoactive drugs are taken with it.

Stimulants

Epidemiological data show increased rates of crashes, injuries and fatalities when methamphetamine[10] or cocaine is present. The stimulant effects may be manifested by speeding, running red lights, aggressive driving, and unsafe overtaking and lane changes. There is no substantial evidence of sustained improvement in performance with methamphetamine or cocaine from epidemiological or on-road driving studies.

The effects of stimulants are biphasic. After the initial stimulatory phase, a period of extreme fatigue may ensue. There is depression and irresistible sleepiness which can reduce cognitive ability and cause drivers to fall asleep suddenly.

While a single low-dose stimulant may increase mental and motor performance in those who are sleep deprived or fatigued, it does not enhance performance in other people. It may improve performance in simple tasks, but not complex divided attention tasks such as driving. As with many other drugs there is no consistent relationship between the blood concentration of a stimulant and the degree of stimulation or crash risk.

Amphetamines are excreted into saliva from blood. They may therefore be present in oral fluid at higher concentrations than in blood.

Medicinal cannabis

Medicinal cannabis was initially intended to only contain cannabidiol which is not psychoactive. Most patients with the conditions for which medical cannabis was originally claimed to be effective are not likely to be driving. Despite this, some medicinal cannabis does contain tetrahydrocannabinol (THC), especially if it has not been obtained from approved sources. THC is known to adversely affect driving skills but, because of its particular pharmacokinetics, its concentration in body fluids is not reliably related to impairment. Its presence at any level is associated with an increased crash risk.[11] The laws relating to THC and driving are therefore not, and have never been, intended to be based on impairment but only on use of an illicit substance. It is illegal to drive with THC in the body regardless of prescription. The person is likely to be impaired in their ability to drive safely and:

- may not be insured in the event of a collision
- may be charged with criminal offences in the event of a collision
- may be charged with having a proscribed substance in their blood while driving.

THC is unlikely to be secreted into saliva from blood to any extent. Oral fluid tests can be positive because of residual THC deposited from cannabis smoke passing through the mouth, but they should not remain positive for more than a few hours after smoking.

The Therapeutic Goods Administration advises that 'Patients should not drive or operate machinery while being treated with medicinal cannabis'.

Combination of substances

It is common to find more than one drug in the body of surviving or dead drivers after a crash. Australian self-reports suggest that the prevalence of drugged driving in conjunction with alcohol may be as high as 4.1% with cannabis, 2.2% with ecstasy, 1.9% with methamphetamine and 0.9% with benzodiazepines.[12]

Co-administration of sedative drugs may cause more profound sedation and effects on driving ability than any drug taken on its own. The synergistic effects of alcohol and cannabis produce greater impairments in driving ability than each substance individually.[13,14] This is due to the effects on different aspects of executive functioning such as cognition, and psychomotor and actual driving performance.

Prescribing regimens that have the least impairing effects on driving ability should always be considered. If prescribing multiple sedating drugs, for example the addition of metoclopramide for acute nausea or sedating antihistamines for hay fever, to other sedative substances, patients must be warned about the effects on driving ability. Cessation of driving may need to be recommended if it is not possible to change to a non-sedating drug.

After effects of drug use

Many substances impair safe driving ability, not only at the time of use, but also afterwards because of a hangover effect. Patients should be warned of these after effects particularly with alcohol and the benzodiazepines, opioids and stimulant drugs.

Rehabilitation

Patients can return to driving after drug or alcohol rehabilitation. At present the Austroads standard requirements[5] are for a conditional licence after a month of remission and an absence of cognitive impairments relevant to driving. There should also be no end-organ effects that impact on driving.

Reporting requirements

Document all discussions with patients with regard to advice on driving and restrictions. Reporting requirements are detailed in Appendix 3 of the Austroads guidelines. Public safety issues must be considered for drivers who are unfit to drive due to medical or medicinal reasons, particularly those patients who may not self-report. In general, no penalties are applied to a prescriber who reports a patient, providing there is no malicious intent.

Conclusion

Driving requires a high level of skill. This may be adversely affected by medical conditions and the drugs used in treatment. Alcohol and illicit substances also impair the ability to drive safely.

When prescribing, consider the effects of the treatment on driving ability. Also enquire about the use of alcohol and other substances. Advise the patient when driving should be avoided or if extra precautions are required. <

Vanita Parekh is Director of the ACT Fitness to Drive Medical Clinic.

REFERENCES

1. Schjerning O, Rosenzweig M, Pottegård A, Damkier P, Nielsen J. Abuse potential of pregabalin: a systematic review. CNS Drugs 2016;30:9-25. https://doi.org/10.1007/s40263-015-0303-6
2. Molero Y, Larsson H, D'Onofrio BM, Sharp DJ, Fazel S. Associations between gabapentinoids and suicidal behaviour, unintentional overdoses, injuries, road traffic incidents, and violent crime: population based cohort study in Sweden. BMJ 2019;365:l2147. https://doi.org/10.1136/bmj.l2147
3. Drummer OH, Yap S. The involvement of prescribed drugs in road trauma. Forensic Sci Int 2016;265:17-21. https://doi.org/10.1016/j.forsciint.2015.12.050
4. Lacherez P, Wood JM, Anstey KJ, Lord SR. Sensorimotor and postural control factors associated with driving safety in a community-dwelling older driver population. J Gerontol A Biol Sci Med Sci 2014;69A:240-4. https://doi.org/10.1093/gerona/glt173
5. Austroads. Assessing fitness to drive: for commercial and private vehicle drivers, 2016. Austroads: Sydney; 2017. https://austroads.com.au/drivers-and-vehicles/assessing-fitness-to-drive
6. Wickens CM, Smart RG, Mann RE. The impact of depression on driver performance. Int J Ment Health Addict 2014;12:524-37. https://doi.org/10.1007/s11469-014-9487-0
7. Dassanayake T, Michie P, Carter G, Jones A. Effects of benzodiazepines, antidepressants and opioids on driving: a systematic review and meta-analysis of epidemiological and experimental evidence. Drug Saf 2011;34:125-56. https://doi.org/10.2165/11539050-000000000-00000
8. Charlton J, Koppel S, Odell M, Devlin A, Langford J, O'Hare M, et al. Influence of chronic illness on crash involvement of motor vehicle drivers: 2nd edition. Clayton (Vic.): Monash University Accident Research Centre; 2010. http://monashuniversity.mobi/muarc/reports/muarc300.html [cited 2019 Nov 1]
9. Wolff K, Brimblecombe R, Forfar JC, Forrest AR, Gilvarry E, Johnston A, et al.; Expert Panel on Drug Driving. Driving under the influence of drugs. London: UK Department for Transport; 2013. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/167971/drug-driving-expert-panel-report.pdf [cited 2019 Nov 1]
10. Logan BK. Methamphetamine and driving impairment. J Forensic Sci 1996;41:457-64. https://doi.org/10.1520/JFS13935J
11. Drummer OH, Gerostamoulos J, Batziris H, Chu M, Caplehorn J, Robertson MD, et al. The involvement of drugs in drivers of motor vehicles killed in Australian road traffic crashes. Accid Anal Prev 2004;36:239-48. https://doi.org/10.1016/S0001-4575(02)00153-7
12. Mallik J, Johnston J, Goren N, Kennedy V. Drugs and driving in Australia. A survey of community attitudes, experience and understanding. Melbourne: Australian Drug Foundation; 2007.
13. Sewell RA, Poling J, Sofuoglu M. The effect of cannabis compared with alcohol on driving. Am J Addict 2009;18:185-93. https://doi.org/10.1080/10550490902786934
14. Downey LA, King R, Papafotiou K, Swann P, Ogden E, Boorman M, et al. The effects of cannabis and alcohol on simulated driving: Influences of dose and experience. Accid Anal Prev 2013;50:879-86. https://doi.org/10.1016/j.aap.2012.07.016

ARTICLE

Atrial fibrillation: an update on management

Craig J McCallum
Cardiology registrar

Deep Chandh Raja
Cardiologist

Rajeev Kumar Pathak
Associate professor

Cardiac Electrophysiology Unit, Department of Cardiology, Canberra Hospital and Health Services, Australian National University

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SUMMARY

Atrial fibrillation carries a markedly increased risk of stroke and left ventricular dysfunction, and is associated with reduced quality of life.

In light of the potential for poor outcomes and the likely understated presence of silent atrial fibrillation, opportunistic screening should be carried out in general practice.

Modifying the risk factors for atrial fibrillation is the cornerstone of management with adjuvant drug therapy to help maintain sinus rhythm, control the ventricular rate and reduce the risk of cerebral thromboembolism.

The need for anticoagulant therapy can be assessed by using the revised CHA_2DS_2-VASc score. Direct oral anticoagulants are now preferred to warfarin in those who qualify for their use.

Catheter ablation is an effective option to improve survival in patients with left ventricular dysfunction. It also improves quality of life and reduces arrhythmia-related hospital admissions.

Introduction

Atrial fibrillation is the most common arrhythmia detected in clinical practice and accounts for over 30% of hospital admissions for cardiac rhythm problems.[1] The burden of disease appears to be increasing with higher prevalence and rates of atrial fibrillation-related hospital admissions. This illustrates the need for a renewed approach to its management.[2]

Epidemiology

The prevalence of atrial fibrillation in Australia is 2–4%, with a predominance in older people.[3] This is likely to be an underestimation because silent atrial fibrillation (asymptomatic, subclinical) has not been taken into account. Most atrial fibrillation in Australia is non-valvular.[4]

Atrial fibrillation is associated with a significant increase in the long-term risk of stroke (2–5-fold higher than matched patients without atrial fibrillation), heart failure, impaired quality of life and all-cause mortality.[1] It is important for GPs to recognise the strong association of certain risk factors with atrial fibrillation. These predominantly include obesity, obstructive sleep apnoea, hypertension,[5,6] valvular heart disease and genetic predisposition.[7,8]

Classification

Classification of atrial fibrillation according to duration of the arrhythmia is shown in Box 1.

Valvular atrial fibrillation is only considered an entity if the patient has moderate to severe mitral stenosis or a mechanical heart valve. All other forms of atrial fibrillation are referred to as 'non-valvular atrial fibrillation'. This distinction influences the choice of anticoagulant therapy.[3]

Screening of patients for atrial fibrillation

Silent atrial fibrillation is present in around 10% of patients who have an ischaemic stroke.[9] Hence all patients with ischaemic stroke should be screened either by a 12-lead ECG or preferably by a 24-hour Holter recording. Monitoring by implanted loop recorders may be a better monitoring strategy especially for candidates with recurrent transient ischaemic attacks and cryptogenic stroke.[10]

Box 1 Classification of atrial fibrillation according to duration

Paroxysmal

Episodes that last less than 7 days, whether they revert spontaneously or undergo direct current cardioversion.

Persistent

Episodes that continue for more than 7 days and do not self-terminate.

Long-standing

Continuous for more than 1 year, despite a rhythm-control strategy.

Permanent

When the patient and the treating physician decide to accept that the patient will remain in atrial fibrillation and will not attempt to achieve sinus rhythm. Often after a rhythm-control strategy has been unsuccessful.

Opportunistic screening (pulse check and ECG) of all patients over the age of 65 years in general practice is now strongly recommended by international guidelines. This follows clear demonstrable benefits to increased quality-adjusted life-years and a reduced incidence of stroke.[11-13] We may soon have eHealth tools like smartphone ECG devices which might contribute to higher detection rates of silent atrial fibrillation.[14,15] However, more research is needed before the routine use of these tools. Also, we need more data to establish the burden of atrial fibrillation detected by these devices before starting therapy.

Diagnostic work up

An ECG is essential to confirm a diagnosis of atrial fibrillation. Additional investigations are needed to determine the cause. All patients should undergo a full blood count, urea and electrolytes and thyroid function tests. An echocardiogram should be performed to detect underlying cardiac abnormalities, such as valvular pathology, left atrial size and volume, as well as the presence of left ventricular dysfunction. In select patients who require acute rhythm control, transoesophageal echocardiography is performed to look for thrombus in the atria before attempting an electrical or pharmacological cardioversion.

Risk stratification tools

The CHA_2DS_2-VASc score is the most widely accepted tool for assessing risk of a stroke in clinical practice and is easy to use. It is endorsed by European[13] and North American guidelines.[16] The 2018 Australian atrial fibrillation guidelines recommend a 'sexless' version of the CHA_2DS_2-VASc score, known as CHA_2DS_2-VA (Table 1).[3] They recommend considering anticoagulation for a CHA_2DS_2-VA score of 1. In contrast, the North American guidelines recommend anticoagulation for a CHA_2DS_2-VASc score of at least 2 in men and at least 3 in women.[3,16] Other risk scores, including ATRIA and ORBIT, do not show major differences in predicting a high risk of stroke.

Bleeding risk can be estimated using the HAS-BLED score (Table 2).[17] Although higher bleeding risk scores can be used to alert the patient and the doctor, they should not discourage anticoagulation. The net benefit to the patient usually favours stroke prevention with anticoagulation over the risk of major bleeding.[3] This requires shared decision making with the patient after discussing the risks and benefits of the treatment strategy.

Treatment strategies

The management of atrial fibrillation revolves around stroke prevention, aggressive risk-factor management, and acute and long-term rate or rhythm control. Catheter ablation may also be considered.

Table 1 **The CHA_2DS_2-VA score**

Risk factor	Definition	Points
C	Congestive heart failure which includes: • symptomatic HFrEF and HFpEF • moderately–severely reduced left ventricular function in the absence of previous symptoms	1
H	Hypertension – whether or not blood pressure is currently elevated	1
A	Age ≥75 years	2
D	Diabetes	1
S	Previous stroke or transient ischaemic attack or history of systemic thromboembolism	2
V	Presence of vascular disease: • previous myocardial infarction, or • peripheral arterial disease, or • complex aortic atheroma or plaque on imaging	1
A	Age 65–74 years	1

Oral anticoagulation therapy to prevent stroke and systemic embolism is recommended in patients with non-valvular atrial fibrillation whose CHA_2DS_2-VA score is ≥2 (high quality of evidence), unless there are contraindications to anticoagulation, and should be considered strongly if CHA_2DS_2-VA score is 1 (moderate quality of evidence).[3]

HFrEF heart failure with reduced ejection fraction
HFpEF heart failure with preserved ejection fraction
Source: reference 3

Table 2 **The HAS-BLED score**

Risk factor	Clinical characteristic	Points
H	Hypertension • systolic blood pressure >160 mmHg	1
A	Abnormal liver OR kidney function • dialysis/renal transplantation/serum creatinine ≥200 mmol/L • cirrhosis or bilirubin 2x upper limit of normal with AST/ALT/ALP 3x upper limit normal	1 each
S	Stroke	1
B	Bleeding • history of bleeding or a bleeding diathesis	1
L	Labile INRs	1
E	Elderly • >65 years	1
D	Drugs OR alcohol • concomitant use of antiplatelets/NSAIDs • ≥8 drinks/week	1 each
HAS-BLED score ≥3 is considered as a high-risk of bleeding		

ALP alkaline phosphatase
ALT alanine aminotransferase
AST aspartate aminotransferase
NSAIDs non-steroidal anti-inflammatory drugs
Source: reference 17

Stroke prevention

Anticoagulation reduces the relative risk of stroke by around 70% in patients with atrial fibrillation. The options include warfarin or direct oral anticoagulant drugs such as factor Xa inhibitors – apixaban and rivaroxaban – and the direct thrombin inhibitor dabigatran. Aspirin is no longer recommended as an alternative.

Direct oral anticoagulants are recommended as first-line therapy over warfarin in patients with non-valvular atrial fibrillation, provided there are no absolute contraindications to their use (see Box 2).[18] Dose reduction of direct oral anticoagulants may also be required depending on patient characteristics (see Table 3).[3] Direct oral anticoagulants are non-inferior to warfarin in reducing the risk of stroke and systemic embolism in these patients and have significantly lower rates of major haemorrhage.[19] Evidence is lacking for their use in patients with mitral stenosis or a metallic valve replacement, hence warfarin is the drug of choice to prevent systemic thromboembolism in this population.

For those receiving warfarin, INR should be measured by routine laboratory tests at least weekly initially and then monthly. Dose modifications of warfarin should be aimed at maintaining the INR between 2 and 3. When switching from warfarin to a direct oral anticoagulant, after warfarin is stopped, the direct oral anticoagulant can be started when the INR is less than 2.[18]

The expert consensus is that patients with concurrent atrial fibrillation and ischaemic heart disease undergoing percutaneous coronary intervention should receive triple therapy with aspirin, clopidogrel and anticoagulation for as short a time as possible (no longer than six months immediately post percutaneous coronary intervention in stable coronary artery disease). They should then continue dual therapy with clopidogrel and anticoagulation for at least 12 months after percutaneous coronary intervention before considering stopping antiplatelet therapy and continuing anticoagulation as monotherapy.[20-23] Current evidence does not support substituting clopidogrel with the newer $P2Y_{12}$ antiplatelet drugs prasugrel and ticagrelor.

Percutaneous left atrial appendage occlusion may be considered as an option in patients with atrial fibrillation at increased risk of stroke who have contraindications to long-term anticoagulation. This is because of the propensity for bleeding or poor drug tolerance.[24]

Box 2 **Absolute contraindications to direct oral anticoagulants**

Severe renal impairment:

- CrCl <30 mL/min with dabigatran
- CrCl <15 mL/min with apixaban*
- CrCl <15 mL/min with rivaroxaban*

Liver impairment e.g. cirrhosis (Child Pugh C)

Current active bleeding or coagulopathy

Previous life-threatening haemorrhage while on a direct oral anticoagulant

Documented previous anaphylaxis to a direct oral anticoagulant

* International European guidelines approve the use of apixaban and rivaroxaban in patients with CrCl as low as 15 mL/min, however this is not reflected in Australian guidance (see Table 3).

CrCl creatinine clearance

Source: reference 18

Table 3 **Dose adjustment of direct oral anticoagulants in non-valvular atrial fibrillation**

Direct oral anticoagulant	Clinical factors	Dose adjustment
Apixaban	At least two of: • serum creatinine ≥133 micromol/L • age ≥80 years • weight ≤60 kg	5 mg twice a day to 2.5 mg twice a day
Rivaroxaban	At least one of: • CrCl 30–49 mL/min • combination with dual antiplatelet therapy	20 mg daily to 15 mg daily
Dabigatran	At least one of: • CrCl 30–50 mL/min • age ≥75 years • combination with dual antiplatelet therapy	150 mg twice a day to 110 mg twice a day

CrCl creatinine clearance

Source: reference 3

Rate control versus rhythm control

To date, randomised controlled trials do not suggest superiority of one strategy over the other.[25]

Rhythm control

Rhythm control may be given priority for:

- those with underlying left ventricular dysfunction
- highly symptomatic patients in spite of rate-control therapy
- patient preference (some patients may not want to remain on rate-control drugs because of their symptoms or intolerance to the drugs)
- paroxysmal or early persistent atrial fibrillation.

In the acute setting, any patient who is haemodynamically unstable should undergo immediate synchronised electrical cardioversion. When the patient is haemodynamically stable, acute rhythm control may be desired if they are symptomatic or if it is their first episode with an onset of less than 48 hours. Flecainide and amiodarone are the two drugs available for acute pharmacological cardioversion.[26]

In patients with haemodynamically stable atrial fibrillation lasting more than 48 hours, or of unknown duration, acute rhythm control should be ideally attempted only after anticoagulation for three weeks. Anticoagulation should be continued for at least four weeks after cardioversion. It is still reasonable to attempt an acute cardioversion, only after the transoesophageal echocardiogram has excluded a left atrial thrombus.[16]

Drugs with the strongest evidence for long-term rhythm control are amiodarone, flecainide and sotalol. Given its high adverse-effect profile, amiodarone is reserved for patients who are highly symptomatic with known left ventricular dysfunction when other drugs could be contraindicated.[3] Flecainide can be started in patients with structurally normal hearts (confirmed with an echocardiogram) who do not have underlying coronary artery disease. Treatment should be started at 50 mg twice a day and titrated up to a maximum dose of 150 mg twice a day, depending on tolerance. Patients should be concomitantly prescribed an atrioventricular nodal blocking drug (e.g. metoprolol) in conjunction with flecainide. Sotalol is also an option for patients intolerant to amiodarone and flecainide. However, the QT interval should be closely monitored, and sotalol is relatively contraindicated in patients with chronic renal impairment.

Rate control

Treatment options for acute rate control are beta blockers, non-dihydropyridine calcium channel antagonists and amiodarone. Again, amiodarone is reserved for patients who are highly symptomatic with known left ventricular dysfunction when other drugs could be contraindicated.

First-line therapies for long-term rate control, in patients without left ventricular dysfunction, are beta blockers (e.g. metoprolol), non-dihydropyridine calcium channel blockers (e.g. verapamil), or digoxin (with monitoring of serum concentrations). The

RACE II trial remains the most recent comprehensive evaluation of strict control.[27] It found that a lenient approach – heart rate target <110 beats per minute – was not associated with worse outcomes than a stricter approach of <80 beats per minute at rest or <110 beats per minute with exercise.[27]

In patients with left ventricular dysfunction who are not being considered for rhythm control, or who have failed rhythm control, first-line rate control therapy would be with beta blockers which have survival benefit in heart failure (e.g. bisoprolol, carvedilol, controlled-release metoprolol or nebivolol), or digoxin. Non-dihydropyridine calcium channel blockers are contraindicated in patients with left ventricular dysfunction.

Risk-factor management

Aggressive management of intercurrent risk factors like obesity, obstructive sleep apnoea, hypertension, diabetes, heart failure, valvular heart disease and excess alcohol is important.[6] Long-term sustained weight loss reduces the burden of atrial fibrillation and maintains sinus rhythm.[28] The Australian guidelines therefore endorse intensive weight loss (at least 10% of body weight) with a target body mass index below 27 kg/m^2.

Exercise is also recommended as it improves aerobic capacity and reduces disease burden. The CARDIO-FIT study showed that arrhythmia-free survival with and without rhythm-control strategies was greatest in patients with high cardiorespiratory fitness compared to adequate or low cardiorespiratory fitness.[29]

Australian guidelines[3] recommend:

- blood pressure no more than 130/80 mmHg at rest, and 200/100 mmHg with exercise
- continuous positive airway pressure therapy if the apnoea–hypopnea index is at least 15/hour
- an HbA1c of no more than 6.5% (48 mmol/mol)
- lipid targets as per the cardiovascular risk profile
- smoking cessation
- no more than three standard drinks of alcohol per week.

Catheter ablation

Catheter ablation delivers radiofrequency energy resulting in isolation of the pulmonary veins and other contiguous venous structures. It has been shown to be a successful therapy in patients with atrial fibrillation.[30] The subgroups that benefit most appear to be patients with paroxysmal and persistent atrial fibrillation who are symptomatic and those with left ventricular dysfunction.[31,32] Catheter ablation also significantly improves quality of life and is associated with significantly fewer hospital admissions.[33] It is important to discuss with the patient that procedural success rates vary and 20–30% of people may require a second procedure within 12 months. Major complication rates from the procedure are 1–7% and are related to the experience of the operator and the centre.[30,31,34] The decision to do catheter ablation should be made after a detailed discussion between the patient and the cardiac specialist.

Conclusion

Treatment strategies for atrial fibrillation include stroke prevention, risk-factor management, rate and rhythm control, and catheter ablation. These have reduced the morbidity and mortality associated with this condition. However, there is growing literature on various aspects of atrial fibrillation management necessitating constant updates for physicians. <

Conflict of interest: none declared

REFERENCES

1. Ball J, Carrington MJ, McMurray JJ, Stewart S. Atrial fibrillation: profile and burden of an evolving epidemic in the 21st century. Int J Cardiol 2013;167:1807-24. https://doi.org/10.1016/j.ijcard.2012.12.093
2. Briffa T, Hung J, Knuiman M, McQuillan B, Chew DP, Eikelboom J, et al. Trends in incidence and prevalence of hospitalization for atrial fibrillation and associated mortality in Western Australia, 1995-2010. Int J Cardiol 2016;208:19-25. https://doi.org/10.1016/j.ijcard.2016.01.196
3. Brieger D, Amerena J, Attia J, Bajorek B, Chan KH, Connell C, et al.; NHFA CSANZ Atrial Fibrillation Guideline Working Group. National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand: Australian clinical guidelines for the diagnosis and management of atrial fibrillation 2018. Heart Lung Circ 2018;27:1209-66. https://doi.org/10.1016/j.hlc.2018.06.1043
4. Raja DC, Kapoor A. Epidemiology of atrial fibrillation - an Indian perspective. J Assoc Physicians India 2016;64(Suppl):7-10.
5. Pathak RK, Mahajan R, Lau DH, Sanders P. The implications of obesity for cardiac arrhythmia mechanisms and management. Can J Cardiol 2015;31:203-10. https://doi.org/10.1016/j.cjca.2014.10.027
6. Pathak RK, Middeldorp ME, Lau DH, Mehta AB, Mahajan R, Twomey D, et al. Aggressive risk factor reduction study for atrial fibrillation and implications for the outcome of ablation: the ARREST-AF cohort study. J Am Coll Cardiol 2014;64:2222-31. https://doi.org/10.1016/j.jacc.2014.09.028
7. Enriquez A, Antzelevitch C, Bismah V, Baranchuk A. Atrial fibrillation in inherited cardiac channelopathies: from mechanisms to management. Heart Rhythm 2016;13:1878-84. https://doi.org/10.1016/j.hrthm.2016.06.008
8. Lau DH, Schotten U, Mahajan R, Antic NA, Hatem SN, Pathak RK, et al. Novel mechanisms in the pathogenesis of atrial fibrillation: practical applications. Eur Heart J 2016;37:1573-81. https://doi.org/10.1093/eurheartj/ehv375
9. Freedman B, Potpara TS, Lip GY. Stroke prevention in atrial fibrillation. Lancet 2016;388:806-17. https://doi.org/10.1016/S0140-6736(16)31257-0
10. Sanna T, Diener HC, Passman RS, Di Lazzaro V, Bernstein RA, Morillo CA, et al.; CRYSTAL AF Investigators. Cryptogenic stroke and underlying atrial fibrillation. N Engl J Med 2014;370:2478-86. https://doi.org/10.1056/NEJMoa1313600

11. Aronsson M, Svennberg E, Rosenqvist M, Engdahl J, Al-Khalili F, Friberg L, et al. Cost-effectiveness of mass screening for untreated atrial fibrillation using intermittent ECG recording. Europace 2015;17:1023-9. https://doi.org/10.1093/europace/euv083
12. Lowres N, Neubeck L, Redfern J, Freedman SB. Screening to identify unknown atrial fibrillation. A systematic review. Thromb Haemost 2013;110:213-22. https://doi.org/10.1160/TH13-02-0165
13. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al.; ESC Scientific Document Group. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J 2016;37:2893-962. https://doi.org/10.1093/eurheartj/ehw210
14. William AD, Kanbour M, Callahan T, Bhargava M, Varma N, Rickard J, et al. Assessing the accuracy of an automated atrial fibrillation detection algorithm using smartphone technology: The iREAD Study. Heart Rhythm 2018;15:1561-5. https://doi.org/10.1016/j.hrthm.2018.06.037
15. Turakhia MP, Desai M, Hedlin H, Rajmane A, Talati N, Ferris T, et al. Rationale and design of a large-scale, app-based study to identify cardiac arrhythmias using a smartwatch: the Apple Heart Study. Am Heart J 2019;207:66-75. https://doi.org/10.1016/j.ahj.2018.09.002
16. January CT, Wann LS, Calkins H, Chen LY, Cigarroa JE, Cleveland JC Jr, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society in collaboration with the Society of Thoracic Surgeons. Circulation 2019;140:e125-51. https://doi.org/10.1161/CIR.0000000000000665
17. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. Chest 2010;138:1093-100. https://doi.org/10.1378/chest.10-0134
18. Heidbuchel H, Verhamme P, Alings M, Antz M, Hacke W, Oldgren J, et al.; European Heart Rhythm Association. European Heart Rhythm Association Practical Guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation. Europace 2013;15:625-51. https://doi.org/10.1093/europace/eut083
19. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet 2014;383:955-62. https://doi.org/10.1016/S0140-6736(13)62343-0
20. Gibson CM, Mehran R, Bode C, Halperin J, Verheugt F, Wildgoose P, et al. An open-label, randomized, controlled, multicenter study exploring two treatment strategies of rivaroxaban and a dose-adjusted oral vitamin K antagonist treatment strategy in subjects with atrial fibrillation who undergo percutaneous coronary intervention (PIONEER AF-PCI). Am Heart J 2015;169:472-8.e5. https://doi.org/10.1016/j.ahj.2014.12.006
21. Cannon CP, Bhatt DL, Oldgren J, Lip GY, Ellis SG, Kimura T, et al.; RE-DUAL PCI Steering Committee and Investigators. Dual antithrombotic therapy with dabigatran after PCI in atrial fibrillation. N Engl J Med 2017;377:1513-24. https://doi.org/10.1056/NEJMoa1708454
22. Lopes RD, Heizer G, Aronson R, Vora AN, Massaro T, Mehran R, et al.; AUGUSTUS Investigators. Antithrombotic therapy after acute coronary syndrome or PCI in atrial fibrillation. N Engl J Med 2019;380:1509-24. https://doi.org/10.1056/NEJMoa1817083
23. Janardan J, Gibbs H. Combining anticoagulation and antiplatelet drugs in coronary artery disease. Aust Prescr 2018;41:111-5. https://doi.org/10.18773/austprescr.2018.039
24. Pison L, Potpara TS, Chen J, Larsen TB, Bongiorni MG, Blomström-Lundqvist C; Scientific Initiative Committee, European Heart Rhythm Association. Left atrial appendage closure-indications, techniques, and outcomes: results of the European Heart Rhythm Association Survey. Europace 2015;17:642-6. https://doi.org/10.1093/europace/euv069
25. Chatterjee S, Sardar P, Lichstein E, Mukherjee D, Aikat S. Pharmacologic rate versus rhythm-control strategies in atrial fibrillation: an updated comprehensive review and meta-analysis. Pacing Clin Electrophysiol 2013;36:122-33. https://doi.org/10.1111/j.1540-8159.2012.03513.x
26. Chevalier P, Durand-Dubief A, Burri H, Cucherat M, Kirkorian G, Touboul P. Amiodarone versus placebo and class Ic drugs for cardioversion of recent-onset atrial fibrillation: a meta-analysis. J Am Coll Cardiol 2003;41:255-62. https://doi.org/10.1016/S0735-1097(02)02705-5
27. Van Gelder IC, Groenveld HF, Crijns HJ, Tuininga YS, Tijssen JG, Alings AM, et al.; RACE II Investigators. Lenient versus strict rate control in patients with atrial fibrillation. N Engl J Med 2010;362:1363-73. https://doi.org/10.1056/NEJMoa1001337
28. Pathak RK, Middeldorp ME, Meredith M, Mehta AB, Mahajan R, Wong CX, et al. Long-term effect of goal-directed weight management in an atrial fibrillation cohort: a long-term follow-up study (LEGACY). J Am Coll Cardiol 2015;65:2159-69. https://doi.org/10.1016/j.jacc.2015.03.002
29. Pathak RK, Elliott A, Middeldorp ME, Meredith M, Mehta AB, Mahajan R, et al. Impact of CARDIOrespiratory FITness on arrhythmia recurrence in obese individuals with atrial fibrillation: The CARDIO-FIT Study. J Am Coll Cardiol 2015;66:985-96. https://doi.org/10.1016/j.jacc.2015.06.488
30. Ganesan AN, Nandal S, Lüker J, Pathak RK, Mahajan R, Twomey D, et al. Catheter ablation of atrial fibrillation in patients with concomitant left ventricular impairment: a systematic review of efficacy and effect on ejection fraction. Heart Lung Circ 2015;24:270-80. https://doi.org/10.1016/j.hlc.2014.09.012
31. Marrouche NF, Brachmann J, Andresen D, Siebels J, Boersma L, Jordaens L, et al.; CASTLE-AF Investigators. Catheter ablation for atrial fibrillation with heart failure. N Engl J Med 2018;378:417-27. https://doi.org/10.1056/NEJMoa1707855
32. Packer DL, Mark DB, Robb RA, Monahan KH, Bahnson TD, Poole JE, et al. CABANA Investigators. Effect of catheter ablation vs antiarrhythmic drug therapy on mortality, stroke, bleeding, and cardiac arrest among patients with atrial fibrillation: the CABANA randomised clinical trial. JAMA 2019;321:1261-74. https://doi.org/10.1001/jama.2019.0693
33. Mark DB, Anstrom KJ, Sheng S, Piccini JP, Baloch KN, Monahan KH, et al.; CABANA Investigators. Effect of catheter ablation vs medical therapy on quality of life among patients with atrial fibrillation: the CABANA randomized clinical trial. JAMA 2019;321:1275-85. https://doi.org/10.1001/jama.2019.0692
34. Verma A, Jiang CY, Betts TR, Chen J, Deisenhofer I, Mantovan R, et al.; STAR AF II Investigators. Approaches to catheter ablation for persistent atrial fibrillation. N Engl J Med 2015;372:1812-22. https://doi.org/10.1056/NEJMoa1408288

ARTICLE

Penicillin allergy: a practical approach to assessment and prescribing

Misha Devchand
Infectious diseases antimicrobial stewardship pharmacist[1,2]

Jason A Trubiano
Director[1]

Postdoctoral fellow [3]

Research fellow[4]

[1] Antimicrobial Stewardship, Drug and Antibiotic Allergy Service and Centre for Antibiotic Allergy and Research, Austin Health

[2] Pharmacy Department, Austin Health

[3] The National Centre for Infections in Cancer, Peter MacCallum Cancer Centre

[4] Department of Medicine, Austin Health, University of Melbourne

Melbourne

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SUMMARY

Penicillin allergies are not always lifelong. Approximately 50% are lost over five years.

A reaction to penicillin during a childhood infection is unlikely to be a true allergy.

Only 1–2% of patients with a confirmed penicillin allergy have an allergy to cephalosporins. In patients with a low risk of severe allergic reactions, cephalosporins are a relatively safe treatment option.

Patients with a history of delayed non-severe reactions, such as mild childhood rashes that occurred over 10 years ago, may be suitable for an oral rechallenge with low-dose penicillin. This should be done in a supervised hospital environment.

In many cases, with appropriate assessment and allergy testing, it may be possible to remove the penicillin allergy label.

Introduction

Most patients who say they have a penicillin allergy are not allergic to penicillins. While 10% of the population will report a penicillin allergy, less than 1% will be truly allergic.[1,2] They have been erroneously labelled as penicillin-allergic.

In the USA, penicillin allergies are the most commonly documented drug allergy, with up to 20% of hospitalised patients having a recorded penicillin allergy.[3,4] In Australian hospitals, national point prevalence data (2013–14) show that 8.9% of patients have a penicillin allergy label on their medical record.[5] A high proportion of these labels are likely to be incorrect. The patient may have had a non-immune-mediated reaction such as nausea and vomiting, an exanthema (e.g. after taking amoxicillin during an Epstein-Barr virus infection) or an injection-site reaction.[6,7]

Impact of allergy labels

Patient-reported penicillin allergies alter antibiotic management and may result in the use of suboptimal or broader spectrum drugs such as fluoroquinolones, macrolides, glycopeptides and cephalosporins.[6,8-11] Having a penicillin allergy label has been associated with an increased risk of *Clostridium difficile*, methicillin-resistant *Staphylococcus aureus* (MRSA), and vancomycin-resistant enterococci infections and colonisation.[3] The increased use of broad-spectrum drugs in hospitalised patients with penicillin allergies also contributes to the growing global problem of antimicrobial resistance.[6,9,12,13] Antibiotic allergy labels are correlated with increases in length of hospital stay,[3] hospital readmission rates,[10] surgical site infections,[14] and admissions to intensive care units.[15] Similarly in general practice, penicillin allergy labels are associated with an increased risk of death and MRSA infection or colonisation.[16]

Impermanent allergy

It has been demonstrated that more than 90% of patients labelled as having a penicillin allergy would be able to tolerate penicillins following appropriate assessment and allergy testing.[17-19] Even penicillin allergies confirmed by skin tests can wane over time. Half the patients who have a positive skin test for penicillins will lose that reactivity after five years.[13,20] There is therefore interest in penicillin allergy 'de-labelling'. This is the removal of the allergy label following either allergy history reconciliation or testing (oral provocation or skin testing).

What is true penicillin allergy?

The classification of a patient-reported penicillin allergy label is the first important step in appropriate care (Table 1). Before prescribing, ask patients about their allergies, as not all allergies may have been documented in their medical records. Conversely, some reactions labelled as allergic may be other types of adverse events. Ask about the clinical features of suspected reactions.

Allergic cross-reactivity

The beta-lactam antibiotics include penicillins, cephalosporins, carbapenems and monobactams. Previously it was thought that patients with penicillin

Table 1 **Antibiotic allergy classifications**

Type	Mechanism	Clinical examples	Common antibiotic examples	Antibiotic recommendation
Type A adverse drug reactions – non-immune-mediated				
Non-severe	Pharmacologically predictable reactions	Nausea, vomiting, diarrhoea, pruritis (without rash), headache	Beta-lactams	Use all antibiotics
Severe		Encephalitis, renal impairment, tendinopathy	Cefepime, aminoglycosides, fluoroquinolones	Only avoid the implicated drug or dose
Type B adverse drug reactions – immune-mediated				
1	IgE-mediated	Urticaria, angioedema, bronchospasm, anaphylaxis	Penicillins, cephalosporins	Avoid implicated drug. Caution with drugs in the same class and structurally related drugs
2	Antibody (usually IgG)-mediated cell destruction	Haemolytic anaemia, thrombocytopenia, vasculitis	Penicillins, cephalosporins	
3	IgG or IgM and complement	Fever, rash, arthralgia	Penicillin, amoxicillin, cefaclor	
4	T-cell mediated	Maculopapular exanthema, drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome, toxic epidermal necrolysis, acute generalised exanthematous pustulosis	Beta-lactams, glycopeptides, sulfonamides	Avoid implicated drug, drugs in the same class and structurally related drugs
Anaphylactoid reactions – non-immune-mediated				
Non-IgE-mediated	Direct mast-cell stimulation or basophil activation	Flushing, itching, urticaria, angioedema	Vancomycin, macrolides, fluoroquinolones	Manage the reaction, either by slowing the infusion or premedication (with antihistamines or corticosteroids)

allergies had a 10% risk of cross-reactivity with cephalosporins and carbapenems.[21] However, reviews have reported that the risk of cross-reactivity between cephalosporins, carbapenems and penicillins may be as low as 1%.[21-24]

The cross-reactivity between beta-lactam antibiotics may be due to the beta-lactam ring itself, an adjacent thiazolidine or dihydrothiazine ring, or from the side chains (R1 in penicillins or R1 and R2 in cephalosporins) – see Fig. 1. True cross-reactivity is largely due to the R1 side chains, with the highest risk being in beta-lactams with identical side chains.

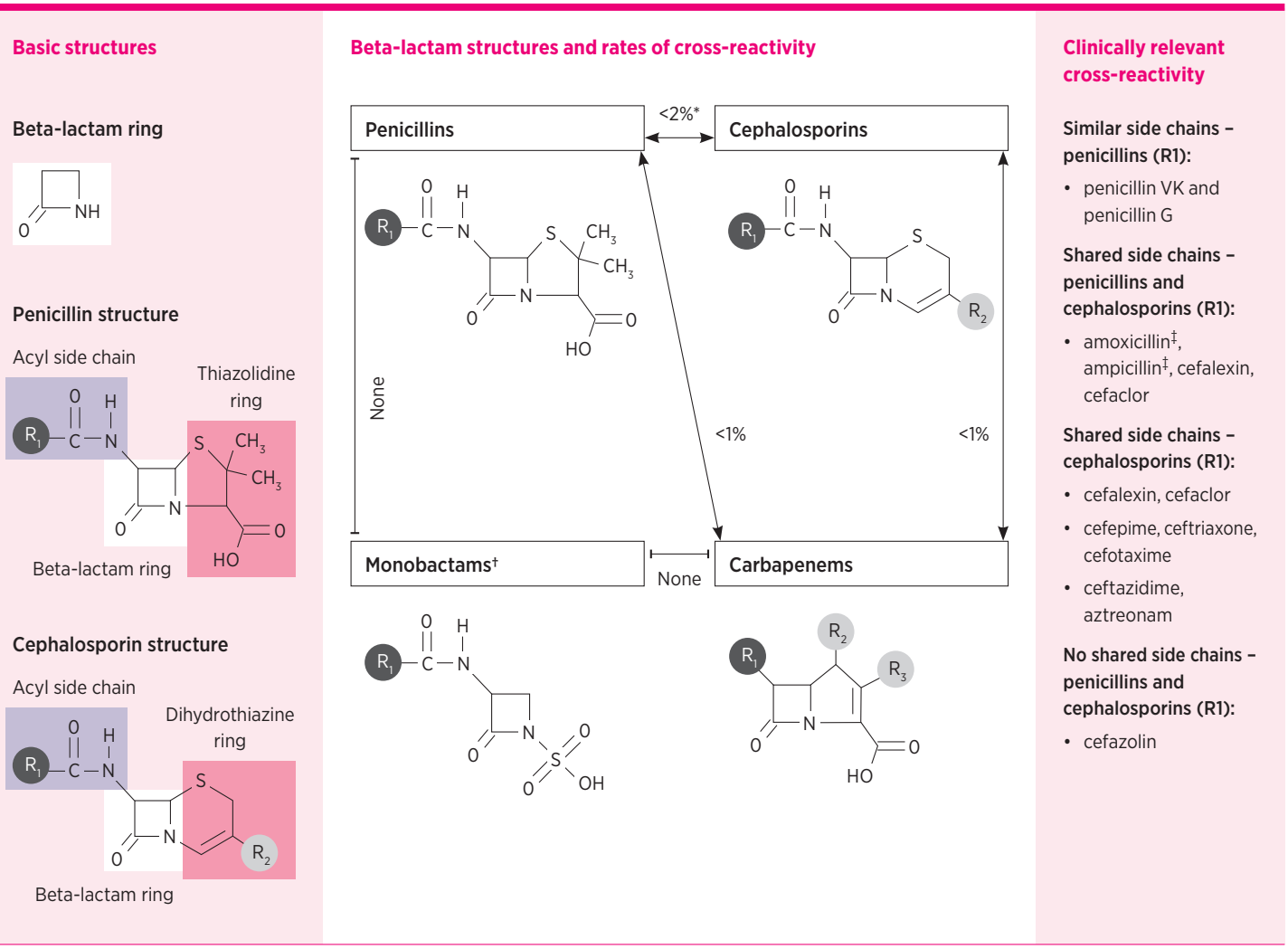
Cross-reactivity is particularly seen with aminopenicillins (amoxicillin, ampicillin) and aminocephalosporins (cefalexin, cefaclor, cefadroxil, ceprozil).[24] The rate of cross-reactivity between aminopenicillins and aminocephalosporins has been reported to be as high as 30–40% in predominately European studies.[23,25-27] At the antibiotic allergy testing centres of Austin Health and the Peter MacCallum Cancer Centre in Melbourne, out of 15 patients reporting a severe-immediate cefalexin hypersensitivity, intradermal tests determined that six (40%) would not be able to tolerate ampicillin.[5,28]

While the data regarding cross-reactivity have primarily been about immediate hypersensitivities, similar patterns have been reported in non-severe delayed penicillin allergies.[29,30] There are limited data regarding cross-reactivity in severe delayed reactions, such as Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms, and acute generalised exanthematous pustulosis. For these severe delayed reactions, information regarding cross-reactivity is not a reliable guide for empirical prescribing.

Assessing penicillin allergies

The key to both prescribing and de-labelling for patients with a history of penicillin allergy is an accurate assessment. This involves an understanding of the allergy particularly the severity, timing and tolerance. Therapeutic Guidelines: Antibiotic contains a guide for this assessment (Fig. 2).[31]

Fig. 1 **Rates of cross-reactivity between beta-lactam antibiotics**



Beta-lactam antibiotics include penicillins, cephalosporins, carbapenems and monobactams.

The left panel shows basic structures of beta-lactam antibiotics. Cross-reactivity is possible through the core beta-lactam ring, adjacent thiazolidine (penicillin) or dihydrothiazine (cephalosporin) ring, and also from a side chain (R1 or R2). Cephalosporins have both R1 and R2 side chains while penicillins only have R1. Despite varied mechanisms, true cross-reactivity is largely based on R1 side chains. Identical side chains in patients with IgE-mediated allergy pose the highest risk. However, cross-reactivity from side chains that are similar, but not identical, and from R2 side chain similarity, is possible and reported.

The centre panel demonstrates the structure and rates of cross-reactivity between penicillins, cephalosporins, carbapenems and monobactams. The right panel details the most clinically important cross-reactivity considerations.

* Except for shared group aminopenicillins and cephalosporins.

† Monobactams have no shared cross-reactivity with other beta-lactams, with the exception for aztreonam and ceftazidime, which share an identical R1.

‡ Amoxicillin and ampicillin are structurally similar aminopenicillins and should be considered clinically cross-reactive with each other and the respective cephalosporins with shared R1 side chains listed in the figure. Similar considerations exist for the aminocephalosporins.

Source: Adapted from Blumenthal et al. (with permission)[22]

Severity

An understanding of the severity of an allergy includes obtaining a description of its 'type'. Information can be obtained by asking about how the reaction was managed, for example, was the patient hospitalised? What treatments were given for the reaction (e.g. adrenaline (epinephrine), antihistamine, systemic steroids or no therapy)? Simply asking the patient if the reaction was 'severe' is unlikely to gather accurate information.

Timing

The timing of the reaction is important to determine if it was delayed (e.g. T-cell mediated reaction) or immediate (e.g. IgE-mediated reaction). Immediate reactions typically occur within a 'few hours' of the first or second dose of the antibiotic. A delayed reaction usually occurs after 'days' of taking the antibiotic and the reaction can be accelerated if the antibiotic is given again.

Fig. 2 **Penicillin allergy assessment guide**

Penicillin allergy assessment guide

NEW UNDERSTANDINGS IN PENICILLIN ALLERGY

1 **Penicillin allergy often wanes over time**
50% of people will no longer be allergic at 5 years.

2 **Many reported penicillin allergies are not true allergies**
Over 90% of reported penicillin allergies can be excluded by skin testing and oral provocation.

3 **Cross-reactivity between penicillins and cephalosporins is less common than previously thought**
Overall, only 1 to 2% of patients with a confirmed penicillin allergy have a cephalosporin allergy.
(However, a reaction to cefalexin or cefaclor is more likely if the patient had a recent amoxicillin or ampicillin allergy, because these drugs have a similar side-chain structure.)

ASSESSING PENICILLIN ALLERGY

Appropriate antibiotic prescribing in a patient reporting a penicillin allergy requires an understanding of allergy SEVERITY (severe vs nonsevere) and TIMING (immediate vs delayed), and antibiotics tolerated since the reaction.

Questions to ask in a penicillin allergy assessment

SEVERITY—severe or nonsevere	1. Do you remember the details of the reaction? 2. How was the reaction managed? Did it require treatment or hospitalisation?
TIMING—immediate (onset within hours of first or second dose) **or delayed** (onset after days); **recent or distant past**	3. How long after taking the antibiotic did the reaction occur? 4. How many years ago did the reaction occur?
ANTIBIOTICS TOLERATED SINCE REACTION	5. Since the reaction, have you taken any other antibiotics without problems? Having tolerated an antibiotic before an allergic reaction does not mean you will tolerate it after the reaction.

If the patient cannot recall the details of the reaction, use the time since reaction (childhood vs recent) and treatment (eg no treatment vs hospitalisation) to gauge the likely severity. Many people who report allergy to a penicillin in childhood are able to tolerate the drug as an adult.

Examples of penicillin allergy, classified by severity and timing

	Severe	Nonsevere
Immediate	anaphylaxis, compromised airway, angioedema, extensive urticaria, hypotension, collapse	mild urticaria or mild immediate rash
Delayed	severe cutaneous adverse drug reactions (eg DRESS, SJS/TEN), or significant internal organ involvement (eg acute interstitial nephritis)	benign childhood rash or maculopapular rash

DRESS = drug rash with eosinophilia and systemic symptoms; SJS/TEN = Stevens–Johnson syndrome / toxic epidermal necrolysis

PRESCRIBING FOR PATIENTS WITH PENICILLIN ALLERGY

If the patient reporting a penicillin allergy cannot recall the details of the reaction, use the information available to assess the level of risk, and weigh up the benefits and harms of prescribing a particular antibiotic. For less severe infections, consider whether an antibiotic is really needed.

While prescribing a non–beta-lactam antibiotic may seem the simplest option, in many cases this is not the optimal treatment for the infection, and it can be associated with a greater risk of adverse reactions and antimicrobial resistance.

Consult *eTG complete* for treatment recommendations and further information:

- antibiotic recommendations for specific infections, based on four categories of penicillin allergy: severe immediate / severe delayed / nonsevere immediate / nonsevere delayed
- a flowchart summarising the management of patients reporting hypersensitivity to penicillins in whom a beta-lactam antibiotic is the preferred drug
- information on beta lactam cross-reactivity. An understanding of penicillins and cephalosporins that share similar side-chain structures is helpful to predict cross-reactivity.

Therapeutic Guidelines — Celebrating Antibiotic Guidelines 40 years 1978–2018 — Centre for Antibiotic Allergy and Research

Ask how many years ago the reaction occurred. This is important for assessing the likelihood that the penicillin allergy has persisted. In patients with true immediate penicillin allergies, the response wanes over time, with 80% of patients becoming tolerant to penicillins after 10 years.[32]

Tolerance

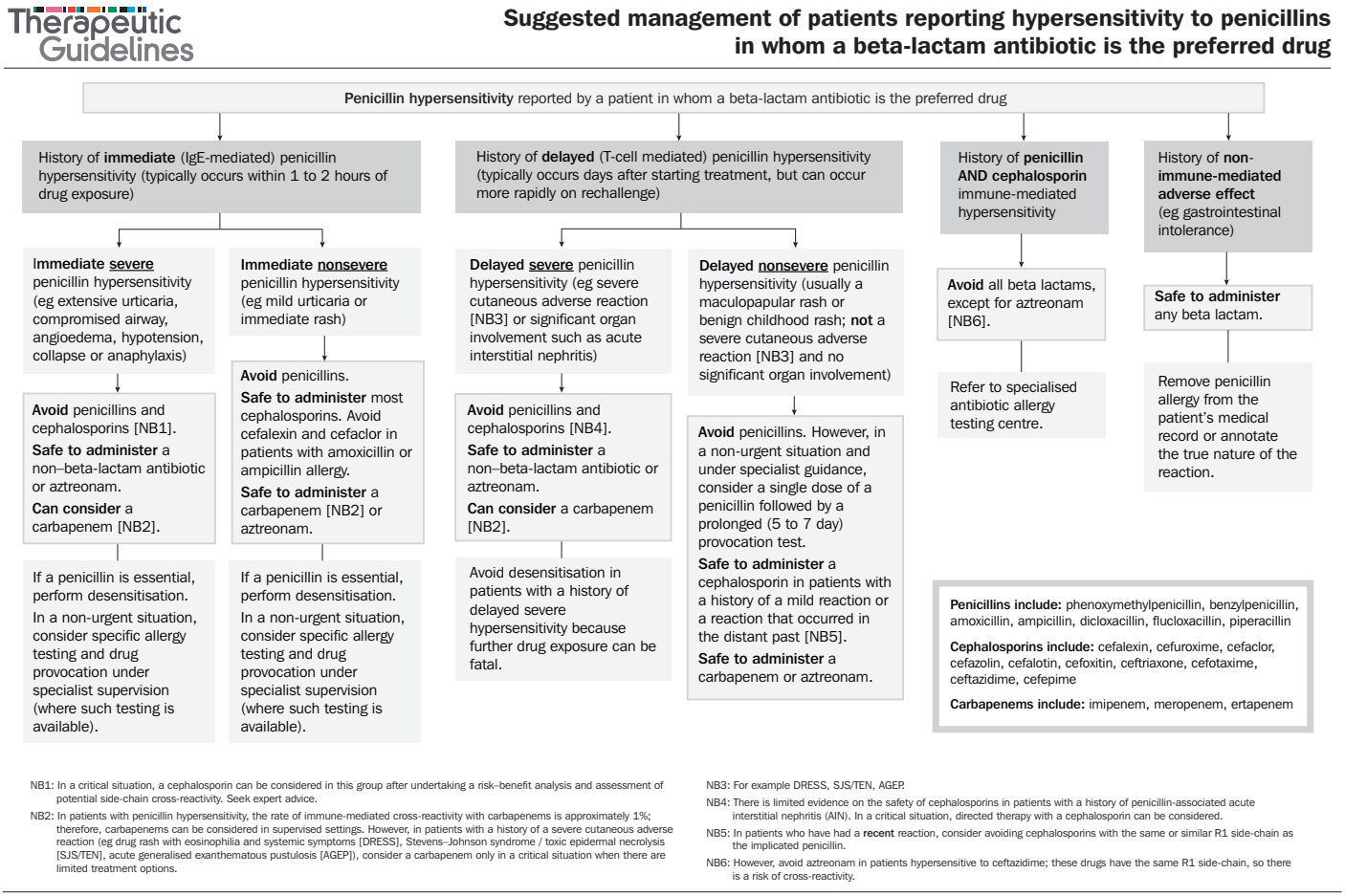
The patient should be questioned about antibiotics that they have tolerated since the reaction, particularly oral penicillins or cephalosporins. Antibiotics that have been tolerated following the reaction should be considered first. Being able to tolerate a specific antibiotic before the reaction does not predict tolerance following the reaction.

Risk assessment

The assessment of penicillin allergy enables classification of phenotypes as either severe versus non-severe and immediate versus delayed. This is helpful in stratifying the risk of using alternative beta-lactam antibiotics. Recommendations for prescribing based on the phenotypes appear in the Therapeutic Guidelines: Antibiotic (Fig. 3).[31]

There are tools that can be used to aid in the assessment of penicillin allergies.[32-34] An example is the Antibiotic Allergy Assessment Tool.[34] This underwent multidisciplinary validation by nursing staff, pharmacists, junior and senior medical staff with no training in allergy. It has subsequently been used

Fig. 3 **Suggested management of patients reporting hypersensitivity to penicillins in whom a beta-lactam antibiotic is the preferred drug**



by hospital pharmacists and nurses to assess beta-lactam allergy labels.[35] This tool classifies penicillin allergies into colour-coded risk groups and suggests an appropriate method for de-labelling:[34,36]

- no risk – direct 'de-label'
- low risk – potential direct oral rechallenge
- moderate risk – formal skin testing required before oral rechallenge
- high risk – formal allergy assessment (may include skin testing).

Table 2 shows an extract of the Antibiotic Allergy Assessment Tool.

De-labelling

Non-immune-mediated adverse drug reactions (type A) are not true allergic reactions. Common examples are gastrointestinal symptoms, such as nausea, vomiting and diarrhoea. If a patient has been labelled as penicillin-allergic because of a type A reaction, this should not stop the prescribing of beta-lactam antibiotics and patients do not need to undergo allergy testing. These labels should be directly removed from the patients' medical records after a discussion about the nature of these reactions and the potential for treatment failure and adverse events if these antibiotics are avoided.

In severe type A reactions, the implicated drug should be avoided. However, it may be possible to use other drugs in the same class.

Sometimes allergies are reported reflecting the history of a family member rather than the patient. These spurious cases of allergy can usually be de-labelled.

Oral rechallenge

If there was a delayed, non-severe reaction (such as mild childhood rashes or a maculopapular rash that occurred over 10 years ago) an oral rechallenge with low-dose penicillin can be considered. Increasing evidence supports this in patients with a low risk of severe reactions, but the rechallenge should be in a supervised hospital environment.[37,38] At present, there is limited evidence for trying an oral rechallenge in general practice.

Table 2 **Extract from the Antibiotic Allergy Assessment Tool**

Clinical manifestation	Recommendation and resultant allergy type
Dermatological	
Childhood exanthem (unspecified)	Unlikely to be significant (non-severe)
Details of rash timing unknown and no severe features or hospitalisation	Unlikely to be significant (non-severe)
Diffuse rash or localised rash with no other symptoms developing >24 hours after starting antibiotic, over 10 years ago	Delayed hypersensitivity (non-severe, low-risk)
Liver	
Hepatic enzyme derangement (does not meet criteria for liver failure or severe injury)	Unlikely to be immune-mediated (non-severe, low-risk)
Neurological or gastrointestinal	
Gastrointestinal symptoms (nausea, vomiting, diarrhoea)	Unlikely to be immune-mediated (non-severe, low-risk)
Neurological or central nervous system manifestation (headache, optic neuritis, confusion, depression, mood disorder, low mood, psychosis)	Unlikely to be immune-mediated (non-severe, low-risk)
Renal	
Renal impairment (does not meet criteria for renal failure or severe injury)	Unlikely to be immune-mediated (non-severe, low-risk)
Unknown reaction	
Unknown reaction >10 years ago or family history of penicillin allergy only	Unlikely to be significant (non-severe, low-risk)

Appropriate for supervised direct oral rechallenge

Appropriate for direct de-labelling – removal of allergy label without testing (oral rechallenge if required)

Note: This extract of the tool does not include clinical manifestations such as angioedema and haematological adverse reactions, which require further investigation.
Source: Reference 34

Considering which penicillin to use in an oral rechallenge is important as patients can retain hypersensitivity to one penicillin (e.g. amoxicillin) while tolerating another (e.g. penicillin VK) due to variations in the antibiotic R1 side chains. Before the widespread use of amoxicillin, most 'penicillin allergies' would be secondary to penicillin VK or G. This should guide the drug to be used for the rechallenge if the 'penicillin' is unspecified. For example, if the patient's allergy dated back to the 1960s, it would be appropriate to use penicillin VK in the rechallenge.

Prescribing for patients with penicillin allergies

Treatment options for patients with a penicillin allergy can be difficult. Prescribing should be guided by the information obtained from a thorough allergy assessment. Detailed advice regarding the use of cephalosporins and carbapenems is given in the Therapeutic Guidelines: Antibiotic (Fig. 3).[31]

Conclusion

While penicillin allergies can be life-threatening, it is important to ensure that all patients with a recorded penicillin allergy label undergo a thorough antibiotic allergy assessment. These labels should be removed if the patient did not have a true immune-mediated reaction. An assessment of the severity, timing and tolerance of allergic reactions will lead to more 'de-labelling' and improved prescribing.

If there has been a presumed immune-mediated reaction, formal antibiotic allergy testing should be considered. While the management of patients with a penicillin allergy can be challenging, the cross-reactivity between penicillins and other beta-lactams is lower than initially reported. In patients with a low risk of severe allergic reactions, cephalosporins can be considered as an appropriate treatment option to penicillins. ◀

Conflicts of interest: none declared

REFERENCES

1. Trubiano JA, Adkinson NF, Phillips EJ. Penicillin allergy is not necessarily forever. JAMA 2017;318:82-3. https://doi.org/10.1001/jama.2017.6510
2. Blumenthal KG, Peter JG, Trubiano JA, Phillips EJ. Antibiotic allergy. Lancet 2019;393:183-98. https://doi.org/10.1016/S0140-6736(18)32218-9
3. Macy E, Contreras R. Health care use and serious infection prevalence associated with penicillin "allergy" in hospitalized patients: A cohort study. J Allergy Clin Immunol 2014;133:790-6. https://doi.org/10.1016/j.jaci.2013.09.021
4. Trubiano JA, Thursky KA, Stewardson AJ, Urbancic K, Worth LJ, Jackson C, et al. Impact of an integrated antibiotic allergy testing program on antimicrobial stewardship: a multicenter evaluation. Clin Infect Dis 2017;65:166-74. https://doi.org/10.1093/cid/cix244
5. Trubiano JA, Chen C, Cheng AC, Grayson ML, Slavin MA, Thursky KA; National Antimicrobial Prescribing Survey (NAPS). Antimicrobial allergy 'labels' drive inappropriate antimicrobial prescribing: lessons for stewardship. J Antimicrob Chemother 2016;71:1715-22. https://doi.org/10.1093/jac/dkw008
6. Sousa-Pinto B, Cardoso-Fernandes A, Araújo L, Fonseca JA, Freitas A, Delgado L. Clinical and economic burden of hospitalizations with registration of penicillin allergy. Ann Allergy Asthma Immunol 2018;120:190-194.e2. https://doi.org/10.1016/j.anai.2017.11.022
7. Knezevic B, Sprigg D, Seet J, Trevenen M, Trubiano J, Smith W, et al. The revolving door: antibiotic allergy labelling in a tertiary care centre. Intern Med J 2016;46:1276-83. https://doi.org/10.1111/imj.13223
8. Sacco KA, Bates A, Brigham TJ, Imam JS, Burton MC. Clinical outcomes following inpatient penicillin allergy testing: a systematic review and meta-analysis. Allergy 2017;72:1288-96. https://doi.org/10.1111/all.13168
9. Sigona NS, Steele JM, Miller CD. Impact of a pharmacist-driven beta-lactam allergy interview on inpatient antimicrobial therapy: a pilot project. J Am Pharm Assoc (2003) 2016;56:665-9. https://doi.org/10.1016/j.japh.2016.05.005
10. MacFadden DR, LaDelfa A, Leen J, Gold WL, Daneman N, Weber E, et al. Impact of reported beta-lactam allergy on inpatient outcomes: a multicenter prospective cohort study. Clin Infect Dis 2016;63:904-10. https://doi.org/10.1093/cid/ciw462
11. Huang KG, Cluzet V, Hamilton K, Fadugba O. The impact of reported beta-lactam allergy in hospitalized patients with hematologic malignancies requiring antibiotics. Clin Infect Dis 2018;67:27-33. https://doi.org/10.1093/cid/ciy037
12. Blumenthal KG, Shenoy ES, Wolfson AR, Berkowitz DN, Carballo VA, Balekian DS, et al. Addressing inpatient beta-lactam allergies: a multihospital implementation. J All Clin Immunol Pract 2017;5:616-25 e7.
13. Chen JR, Tarver SA, Alvarez KS, Tran T, Khan DA. A proactive approach to penicillin allergy testing in hospitalized patients. J Allergy Clin Immunol Pract 2017;5:686-93. https://doi.org/10.1016/j.jaip.2016.09.045
14. Blumenthal KG, Ryan EE, Li Y, Lee H, Kuhlen JL, Shenoy ES. The impact of a reported penicillin allergy on surgical site infection risk. Clin Infect Dis 2018;66:329-36. https://doi.org/10.1093/cid/cix794
15. Charneski L, Deshpande G, Smith SW. Impact of an antimicrobial allergy label in the medical record on clinical outcomes in hospitalized patients. Pharmacotherapy 2011;31:742-7. https://doi.org/10.1592/phco.31.8.742
16. West RM, Smith CJ, Pavitt SH, Butler CC, Howard P, Bates C, et al. 'Warning: allergic to penicillin': association between penicillin allergy status in 2.3 million NHS general practice electronic health records, antibiotic prescribing and health outcomes. J Antimicrob Chemother 2019;74:2075-82. https://doi.org/10.1093/jac/dkz127
17. Bourke J, Pavlos R, James I, Phillips E. Improving the effectiveness of penicillin allergy de-labeling. J Allergy Clin Immunol Pract 2015;3:365-74.e1. https://doi.org/10.1016/j.jaip.2014.11.002
18. Macy E, Ngor EW. Safely diagnosing clinically significant penicillin allergy using only penicilloyl-poly-lysine, penicillin, and oral amoxicillin. J Allergy Clin Immunol Pract 2013;1:258-63. https://doi.org/10.1016/j.jaip.2013.02.002
19. Chen JR, Khan DA. Evaluation of penicillin allergy in the hospitalized patient: opportunities for antimicrobial stewardship. Curr Allergy Asthma Rep 2017;17:40. https://doi.org/10.1007/s11882-017-0706-1
20. Blanca M, Torres MJ, García JJ, Romano A, Mayorga C, de Ramon E, et al. Natural evolution of skin test sensitivity in patients allergic to beta-lactam antibiotics. J Allergy Clin Immunol 1999;103:918-24. https://doi.org/10.1016/S0091-6749(99)70439-2
21. Campagna JD, Bond MC, Schabelman E, Hayes BD. The use of cephalosporins in penicillin-allergic patients: a literature review. J Emerg Med 2012;42:612-20. https://doi.org/10.1016/j.jemermed.2011.05.035
22. Blumenthal KG, Peter JG, Trubiano JA, Phillips EJ. Antibiotic allergy. Lancet 2019;393:183-98. https://doi.org/10.1016/S0140-6736(18)32218-9

23. Romano A, Valluzzi RL, Caruso C, Maggioletti M, Quaratino D, Gaeta F. Cross-reactivity and tolerability of cephalosporins in patients with IgE-mediated hypersensitivity to penicillins. J Allergy Clin Immunol Pract 2018;6:1662-72. https://doi.org/10.1016/j.jaip.2018.01.020
24. Trubiano JA, Stone CA, Grayson ML, Urbancic K, Slavin MA, Thursky KA, et al. The 3 Cs of antibiotic allergy-classification, cross-reactivity, and collaboration. J Allergy Clin Immunol Pract 2017;5:1532-42. https://doi.org/10.1016/j.jaip.2017.06.017
25. Phillips E, Knowles SR, Weber EA, Blackburn D. Cephalexin tolerated despite delayed aminopenicillin reactions. Allergy 2001;56:790. https://doi.org/10.1034/j.1398-9995.2001.056008790.x
26. Romano A, Gaeta F, Arribas Poves MF, Valluzzi RL. Cross-reactivity among beta-lactams. Curr Allergy Asthma Rep 2016;16:24. https://doi.org/10.1007/s11882-016-0594-9
27. Miranda A, Blanca M, Vega JM, Moreno F, Carmona MJ, García JJ, et al. Cross-reactivity between a penicillin and a cephalosporin with the same side chain. J Allergy Clin Immunol 1996;98:671-7. https://doi.org/10.1016/S0091-6749(96)70101-X
28. Trubiano JA, Tan N, Douglas A, Holmes NE, Chua K, Stevenson W, et al., editors. The impacts of an AMS-led antibiotic allergy testing program – a tertiary referral centre experience. ASID Annual Scientific Meeting 2019; 2019 May 16–18; Darwin, Australia.
29. Romano A, Gaeta F, Valluzzi RL, Maggioletti M, Caruso C, Quaratino D. Cross-reactivity and tolerability of aztreonam and cephalosporins in subjects with a T cell-mediated hypersensitivity to penicillins. J Allergy Clin Immunol 2016;138:179-86. https://doi.org/10.1016/j.jaci.2016.01.025
30. Romano A, Gaeta F, Valluzzi RL, Alonzi C, Maggioletti M, Zaffiro A, et al. Absence of cross-reactivity to carbapenems in patients with delayed hypersensitivity to penicillins. Allergy 2013;68:1618-21. https://doi.org/10.1111/all.12299
31. Antimicrobial hypersensitivity [published 2019 Apr; amended 2019 Dec]. In: eTG complete [Internet]. Melbourne: Therapeutic Guidelines Limited; 2019. www.tg.org.au
32. Shenoy ES, Macy E, Rowe T, Blumenthal KG. Evaluation and management of penicillin allergy: a review. JAMA 2019;321:188-99. https://doi.org/10.1001/jama.2018.19283
33. Chiriac AM, Banerji A, Gruchalla RS, Thong BY, Wickner P, Mertes PM, et al. Controversies in drug allergy: drug allergy pathways. J Allergy Clin Immunol Pract 2019;7:46-60.e4. https://doi.org/10.1016/j.jaip.2018.07.037
34. Devchand M, Urbancic KF, Khumra S, Douglas AP, Smibert O, Cohen E, et al. Pathways to improved antibiotic allergy and antimicrobial stewardship practice: the validation of a beta-lactam antibiotic allergy assessment tool. J Allergy Clin Immunol Pract 2019;7:1063-1065.e5. https://doi.org/10.1016/j.jaip.2018.07.048
35. Devchand M, Kirkpatrick CM, Stevenson W, Garrett K, Perera D, Khumra S, et al. Evaluation of a pharmacist-led penicillin allergy de-labelling ward round: a novel antimicrobial stewardship intervention. J Antimicrob Chemother 2019;74:1725-30. https://doi.org/10.1093/jac/dkz082
36. Brockow K. Triage strategies for clarifying reported betalactam allergy. J Allergy Clin Immunol Pract 2019;7:1066-7. https://doi.org/10.1016/j.jaip.2018.08.009
37. Trubiano JA, Smibert O, Douglas A, Devchand M, Lambros B, Holmes NE, et al. The safety and efficacy of an oral penicillin challenge program in cancer patients: a multicenter pilot study. Open Forum Infect Dis 2018;5:ofy306. https://doi.org/10.1093/ofid/ofy306
38. Banks TA, Tucker M, Macy E. Evaluating penicillin allergies without skin testing. Curr Allergy Asthma Rep 2019;19:27. https://doi.org/10.1007/s11882-019-0854-6

FURTHER READING

Yuson CL, Katelaris CH, Smith WB. 'Cephalosporin allergy' label is misleading. Aust Prescr 2018;41:37-41. https://doi.org/10.18773/austprescr.2018.008

ARTICLE

The 2018 Aged Care National Antimicrobial Prescribing Survey: results show room for improvement

Leslie Dowson[1,2]
Arjun Rajkhowa[2,3]
Kirsty Buising[2,3,4]
David CM Kong[1,2,5]
Rhonda L Stuart[1,2,6]
Karin Thursky[2,3,7]
Noleen Bennett[2,3,8]

[1] Monash University
[2] National Centre for Antimicrobial Stewardship, Melbourne
[3] University of Melbourne
[4] Victorian Infectious Diseases Service, Melbourne
[5] Ballarat Health Services, Ballarat
[6] Monash Health, Clayton
[7] Peter MacCallum Cancer Centre, Melbourne
[8] Victorian Healthcare Associated Infection Surveillance System Coordinating Centre, Melbourne
Victoria

Full author details are available online.

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SUMMARY

The annual Aged Care National Antimicrobial Prescribing Survey aims to identify local and national prescribing issues and guide antimicrobial stewardship goals.

In the 2018 point prevalence survey, medication charts of over 20,000 residents were reviewed from 407 participating facilities across Australia.

On the day of the survey, almost 10% of residents were prescribed an antimicrobial.

Nearly two-thirds of recently prescribed antimicrobials were for residents who had no documented signs or symptoms of infection.

Over a quarter of antimicrobials had been prescribed for longer than six months.

Incomplete documentation was a prominent barrier to proper review of antimicrobial therapy, with the indication, review date or stop date not documented for many prescriptions.

Recommendations include using appropriate microbiological testing to guide prescribing, following national antimicrobial prescribing guidelines, documenting the indication for the antimicrobial, and its start, stop and review dates, and monitoring and re-evaluating long-term antimicrobial use.

Introduction

Residents of aged-care homes are especially vulnerable to infection.[1] Lack of diagnostic certainty can compound the complexity of decision making around antimicrobial use.[2] In aged-care homes, antimicrobial use takes place within a context of heightened risk and vigilance due to the potential for complications and clinical deterioration.

Overuse and inappropriate use of antimicrobials, however, can accelerate antimicrobial resistance and increase morbidity and mortality from drug-resistant infections. Inappropriate use of antimicrobials can directly and indirectly harm residents,[3] and aged-care homes can serve as reservoirs and sites of transmission of drug-resistant organisms.[4,5] Aged-care homes play an important role in community–hospital transmission of drug-resistant organisms,[6] so prudent use of antimicrobials is a necessity. Surveillance of antimicrobial use can guide improved prescribing practices.

The 2018 Aged Care National Antimicrobial Prescribing Survey

The Aged Care National Antimicrobial Prescribing Survey (AC NAPS) is an annual survey of infections and antimicrobial prescribing practices in Australian aged-care homes and multipurpose services.[7] Its primary aim is to assist participating facilities to reduce infections and improve their use of antimicrobials.

AC NAPS is a point prevalence survey. De-identified data are collected from residents' medical records and entered into an online AC NAPS database by participating nurses, pharmacists or infection-control nurse consultants. The first survey was piloted nationally in 2015,[8] and was followed by surveys in 2016,[9] 2017[10] and 2018[11]. The survey has consistently highlighted aspects of antimicrobial use in aged-care facilities that could be improved.

In 2018, the medication charts of 20,030 permanent, respite or transitional aged-care residents from 407 facilities were reviewed. Facilities from every state and territory in Australia participated. Victorian, state-government-operated, and major city and inner-regional facilities contributed proportionally more data to the survey than their actual representation in the Australian aged-care sector.

Significant results of the survey

On the day of the survey, the following results were found:

- Almost 10% (1988/20,030) of residents were prescribed at least one antimicrobial while only 2.9% (581/20,030) had signs or symptoms of infection.

- Nearly 65% (64.6%, 1009/1563) of recently prescribed antimicrobials were for residents who did not have documented signs or symptoms of suspected infection in the week before they started treatment.
- Over a quarter (28.3%, 663/2341) of antimicrobials had been administered for longer than six months.
- Topical antimicrobials made up over one-third (36.3%, 849/2341) of antimicrobials prescribed.
- Incomplete documentation was a prominent barrier to proper review of medicines. The indication for the antimicrobial was not documented in a quarter of prescriptions (25.1%, 587/2341), and the review date or stop date was not documented for 58.9% (1380/2341) of prescriptions.
- Other – skin, soft tissue or mucosal (18.3%, 428/2341), cystitis (16%, 375/2341) and pneumonia (9.4%, 221/2341) were the three most common indications presumed or documented for antimicrobials prescribed.
- Cefalexin (20.3%, 475/2341) was the most commonly prescribed antimicrobial, followed by clotrimazole (19%, 444/2341).

These findings show there is scope for improvement. The discrepancy between the proportion of residents who were prescribed antimicrobials and the proportion who were identified as having signs or symptoms of infection presents a potential target for quality improvement. In the latter group, the proportion of residents whose suspected infections met infection criteria was only 22.1% (346/1563).

The observed widespread practice of prolonged antimicrobial use (including for prophylaxis) was surprising and suggests that more frequent review and re-evaluation of antimicrobial therapy is required. The findings of the survey may relate to wider system issues such as fragmented access to visiting medical staff and lack of continuity of care.[12]

The findings also point to priority infections in this setting and the antimicrobials that are being used for treatment. The results could be used to help guide clinical education on these specific conditions.

How does practice compare to guidelines?

Empiric antimicrobial use should be in accordance with recommendations in endorsed national prescribing guidelines.[13,14] However, non-concordant use frequently occurs in many Australian aged-care homes. For example, for community-acquired lower respiratory tract infections, amoxicillin with clavulanic acid is repeatedly chosen as a first-line antimicrobial by some prescribers,[15] despite it being recommended as second-line therapy. For skin and soft tissue infections, antimicrobial choices are generally concordant with endorsed national prescribing guidelines when an indication is documented. However, most often, prescribers do not document the indication.[16]

Recommendations to improve antimicrobial use

General principles for improving antimicrobial use in aged-care homes include the following:

- All health professionals should have easy access to endorsed national prescribing guidelines.[13,14] Therapeutic Guidelines: Antibiotic has recently been updated.[13] These should be used to guide antimicrobial prescribing.
- Advance care planning documentation should be consulted, as necessary.[13]
- Clinical care in aged-care homes should meet the Antimicrobial Stewardship Clinical Care Standard.[17]
- The indication for antimicrobial use, and start, stop and review dates should all be clearly documented in the resident's medical record.[17]
- Antimicrobial review plans and actions, including monitoring the resident's clinical condition, reviewing the results of any investigations and appropriately adjusting any therapy, should be documented in the resident's medical record and followed.[17]
- Prolonged antimicrobial use should be avoided. If it is required, residents should be closely monitored and their therapy regularly re-evaluated.[17]
- System-wide issues regarding access to, and continuity of, medical care for aged-care home residents should be addressed.[12]

While local issues can be identified through participation in the AC NAPS, there are also some well-researched and widely known issues with antimicrobial use in aged-care homes that have been identified more broadly. One such issue is the frequent and unnecessary testing of urine specimens, which can lead to unnecessary antimicrobial prescribing.[18,19] In aged-care homes, urinalysis and urine cultures are only appropriate when a resident has symptoms of a urinary tract infection. This may include specific and non-specific symptoms.[13] Cloudy or malodorous urine alone is not a sufficient reason to perform urinalysis or urine cultures, or to prescribe an antimicrobial.[13]

Recommendations to improve antimicrobial use for common infections in aged care are listed in the Table. Links to essential resources for antimicrobial stewardship initiatives have been compiled by the Australian Government.[20]

Standards for antimicrobial stewardship

With the newly updated Aged Care Quality Standards, Australian aged-care homes are now required to demonstrate that they have infection-control practices in place, and 'practices to promote appropriate antimicrobial prescribing and use to support optimal care'.[21] It is hoped that more aged-care homes will incorporate antimicrobial stewardship into their quality and safety framework, and actively engage in surveillance and other quality improvement activities.

Quality agencies have also been promoting the implementation of antimicrobial stewardship programs in aged-care homes through the Antimicrobial Stewardship Clinical Care Standard.[17] This provides guidance on the quality of care that residents and families should expect to receive for an infection. It includes recommendations about antimicrobial use and treatment, such as the use of broad-spectrum antibiotics, and the review of treatment.

Conclusion

Improving the safety and quality of care in the aged-care sector is a national priority.[22] It is important that the quality use of medicines is consistently promoted through existing and emerging quality improvement paradigms.

By participating in the AC NAPS survey, each facility can generate customised reports and examine their local issues. These reports may serve as a basis for educating staff, residents and their families about antimicrobial use and provide an incentive to make clinical policy and practice changes. They can be presented to accreditation organisations as evidence of quality improvement initiatives. Considered together, these approaches are anticipated to yield better outcomes for residents. <

David Kong has sat on advisory boards for Becton Dickinson and MSD, and has received financial travel support from MSD, all of which was unrelated to the current work.

The Aged Care National Antimicrobial Prescribing Survey is coordinated by the National Centre for Antimicrobial Stewardship in partnership with the Guidance Group (Melbourne Health) and the VICNISS Coordinating Centre (Melbourne Health). It is supported by the Australian Commission on Safety and Quality in Health Care as part of the Antimicrobial Use and Resistance in Australia project.[7]

Table **Recommendations to improve antimicrobial use for common infections in aged-care homes**

Infection	Recommendation
Urinary tract	• Urinalysis and urine cultures are only appropriate when a resident has symptoms of a urinary tract infection, such as acute dysuria.[13] • Cloudy or malodorous urine alone is not a sufficient reason to perform urinalysis or urine cultures, or to prescribe an antimicrobial.[13] • Comprehensive investigation and treatment algorithms for urinary tract infections in aged-care homes are available.[13] • Cefalexin is no longer the antimicrobial of choice for acute cystitis.[13] The recommended first-line empiric therapy in non-pregnant women and men is trimethoprim or nitrofurantoin.[13] If cefalexin is prescribed, the dosing and frequency of administration should be concordant with the recommendations.[13,14]
Respiratory tract	• Comprehensive guidance on managing respiratory tract infections in aged-care home residents is available.[13,14] • Polymerase chain reaction testing in residents with signs and symptoms of influenza-like illness or lower respiratory tract infection is recommended.[13,15] • Amoxicillin with clavulanic acid should be reserved as a second-line antimicrobial for community-acquired lower respiratory tract infection.[13] The recommended first-line empiric therapy for community-acquired lower respiratory tract infection is amoxicillin (or doxycycline or cefuroxime for residents with penicillin hypersensitivity).[13]
Skin, soft tissue and mucosal	• The indication for any antimicrobial use, including creams and drops, should be properly documented.[16,17] • If topical antimicrobials are initiated 'when required' by the nursing staff, residents should be reviewed by a medical doctor.[17]

REFERENCES

1. Australian Institute of Health and Welfare. Older Australia at a glance. Canberra: AIHW; 2018. https://www.aihw.gov.au/reports/older-people/older-australia-at-a-glance/contents/health-aged-care-service-use [cited 2019 Nov 1]
2. Nicolle LE, Yoshikawa TT. Urinary tract infection in long-term-care facility residents. Clin Infect Dis 2000;31:757-61. https://doi.org/10.1086/313996
3. Daneman N, Bronskill SE, Gruneir A, Newman AM, Fischer HD, Rochon PA, et al. Variability in antibiotic use across nursing homes and the risk of antibiotic-related adverse outcomes for individual residents. JAMA Intern Med 2015;175:1331-9. https://doi.org/10.1001/jamainternmed.2015.2770
4. Lim CJ, Cheng AC, Kennon J, Spelman D, Hale D, Melican G, et al. Prevalence of multidrug-resistant organisms and risk factors for carriage in long-term care facilities: a nested case-control study. J Antimicrob Chemother 2014;69:1972-80. https://doi.org/10.1093/jac/dku077
5. Stuart RL, Kotsanas D, Webb B, Vandergraaf S, Gillespie EE, Hogg GG, et al. Prevalence of antimicrobial-resistant organisms in residential aged care facilities. Med J Aust 2011;195:530-3. https://doi.org/10.5694/mja11.10724
6. Wang J, Foxman B, Mody L, Snitkin ES. Network of microbial and antibiotic interactions drive colonization and infection with multidrug-resistant organisms. Proc Natl Acad Sci USA 2017;114:10467-72. https://doi.org/10.1073/pnas.1710235114
7. Australian Commission on Safety and Quality in Health Care. Antimicrobial prescribing in Australian residential aged-care. Sydney: ACSQHC; 2019. https://www.safetyandquality.gov.au/our-work/antimicrobial-resistance/antimicrobial-use-and-resistance-australia-surveillance-system-aura/antimicrobial-prescribing-australian-residential-aged-care [cited 2019 Nov 1]
8. National Centre for Antimicrobial Stewardship and Australian Commission on Safety and Quality in Health Care. Antimicrobial prescribing and infections in Australian residential aged care facilities: results of the 2015 Aged Care National Antimicrobial Prescribing Survey pilot. Sydney: Commonwealth of Australia; 2016. https://www.safetyandquality.gov.au/publications-and-resources/resource-library/antimicrobial-prescribing-and-infections-australian-residential-aged-care-facilities-results-2015-aged-care-national-antimicrobial-prescribing-survey-pilot [cited 2019 Nov 1]
9. National Centre for Antimicrobial Stewardship and Australian Commission on Safety and Quality in Health Care. Aged Care National Antimicrobial Prescribing Survey report 2016. Sydney: ACSQHC; 2017. https://www.safetyandquality.gov.au/publications-and-resources/resource-library/2016-aged-care-national-antimicrobial-prescribing-survey-report [cited 2019 Nov 1]
10. National Centre for Antimicrobial Stewardship and Australian Commission on Safety and Quality in Health Care. Antimicrobial prescribing and infections in Australian aged care homes: results of the 2017 Aged Care National Antimicrobial Prescribing Survey. Sydney: ACSQHC; 2018. https://www.safetyandquality.gov.au/publications-and-resources/resource-library/2017-aged-care-national-antimicrobial-prescribing-survey-report [cited 2019 Nov 1]
11. National Centre for Antimicrobial Stewardship and Australian Commission on Safety and Quality in Health Care. Antimicrobial prescribing and infections in Australian aged care homes: results of the 2018 Aged Care National Antimicrobial Prescribing Survey. Sydney: ACSQHC; 2019. https://www.safetyandquality.gov.au/publications-and-resources/resource-library/2018-aged-care-national-antimicrobial-prescribing-survey-report [cited 2019 Nov 1]
12. Lim CJ, Kwong M, Stuart RL, Buising KL, Friedman ND, Bennett N, et al. Antimicrobial stewardship in residential aged care facilities: need and readiness assessment. BMC Infect Dis 2014;14:410. https://doi.org/10.1186/1471-2334-14-410
13. Antibiotic. In eTG complete [Internet]. Melbourne: Therapeutic Guidelines Ltd; 2019. www.tg.org.au [cited 2019 Nov 1]
14. AMH Aged Care Companion [Internet]. Adelaide: Australian Medicines Handbook Pty Ltd; 2019. https://agedcare.amh.net.au [cited 2019 Nov 1]
15. Dowson L, Marshall C, Buising K, Friedman ND, Kong DC, Stuart RL. Optimizing treatment of respiratory tract infections in nursing homes: nurse-initiated polymerase chain reaction testing. Am J Infect Control 2019;47:911-5. https://doi.org/10.1016/j.ajic.2019.02.001
16. Bennett NJ, Imam N, Ingram RJ, James RS, Buising KL, Bull AL, et al. Skin and soft tissue infections and current antimicrobial prescribing practices in Australian aged care residents. Epidemiol Infect 2019;147:e87. https://doi.org/10.1017/S0950268819000128
17. Australian Commission on Safety and Quality in Health Care. Antimicrobial stewardship clinical care standard. Sydney: ACSQHC; 2014. https://www.safetyandquality.gov.au/our-work/clinical-care-standards/antimicrobial-stewardship-clinical-care-standard [cited 2019 Nov 1]
18. Abrutyn E, Mossey J, Berlin JA, Boscia J, Levison M, Pitsakis P, et al. Does asymptomatic bacteriuria predict mortality and does antimicrobial treatment reduce mortality in elderly ambulatory women? Ann Intern Med 1994;120:827-33. https://doi.org/10.7326/0003-4819-120-10-199405150-00003
19. Nicolle LE, Mayhew WJ, Bryan L. Prospective randomized comparison of therapy and no therapy for asymptomatic bacteriuria in institutionalized elderly women. Am J Med 1987;83:27-33. https://doi.org/10.1016/0002-9343(87)90493-1
20. Antimicrobial stewardship [Internet]. Canberra: Antimicrobial Resistance, Australian Government; 2017. https://www.amr.gov.au/what-you-can-do/aged-care/antibiotic-stewardship [cited 2019 Nov 1]
21. Aged care quality standards. Canberra: Australian Government Department of Health; 2019 https://agedcare.health.gov.au/quality/aged-care-quality-standards [cited 2019 Nov 1]
22. Aged care reforms. Canberra: Australian Government Department of Human Services; 2019. https://www.humanservices.gov.au/organisations/health-professionals/subjects/aged-care-reforms [cited 2019 Nov 1]

FURTHER READING

NPS MedicineWise Learning. Urinary tract infections in residential aged-care facilities. Sydney: NPS MedicineWise; 2019. https://learn.nps.org.au/mod/page/view.php?id=6026 [cited 2019 Nov 1]

FEATURE

Top 10 drugs 2018–19

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https://doi.org/10.18773/austprescr.2019.073

Tables 1–3 show the top 10 drugs for the year July 2018 – June 2019. The figures are based on PBS and RPBS prescriptions from the date of supply. The figures include prescriptions under the co-payment (non-subsidised).

Table 1 **Top 10 PBS/RPBS drugs by DDD/1000 population/day**

	Drug	DDD/1000 pop/day*
1.	atorvastatin	71.35
2.	rosuvastatin	57.44
3.	perindopril	51.67
4.	amlodipine	47.95
5.	candesartan	32.90
6.	irbesartan	31.48
7.	telmisartan	31.26
8.	esomeprazole	27.62
9.	ramipril	26.97
10.	metformin	25.14

Table 2 **Top 10 PBS/RPBS drugs by prescription counts**

	Drug	Prescriptions
1.	rosuvastatin	12,026,655
2.	atorvastatin	10,967,105
3.	esomeprazole	9,278,125
4.	pantoprazole	7,375,606
5.	perindopril	6,551,571
6.	cefalexin	5,643,287
7.	amoxicillin	5,254,811
8.	metformin	5,017,700
9.	amoxicillin + clavulanic acid	4,706,645
10.	escitalopram	4,533,725

Table 3 **Top 10 PBS/RPBS drugs by cost to government (does not include rebates)**

	Drug	Cost to government	DDD/1000 pop/day*	Prescriptions
1.	sofosbuvir + velpatasvir†	$391,007,833	‡	25,447
2.	aflibercept	$358,636,721	‡	289,522
3.	adalimumab	$317,436,175	0.74	246,220
4.	nivolumab	$267,738,344	‡	53,861
5.	pembrolizumab	$220,469,394	‡	25,676
6.	denosumab	$218,970,118	16.80	786,535
7.	ranibizumab	$207,163,441	‡	180,721
8.	ustekinumab	$178,790,589	0.44	25,731
9.	glecaprevir + pibrentasvir†	$173,610,672	‡	9,207
10.	apixaban	$170,049,351	5.55	2,088,604

DDD defined daily dose

PBS Pharmaceutical Benefits Scheme

RPBS Repatriation Pharmaceutical Benefits Scheme

* DDD/1000 population/day is a more useful measure of drug utilisation than prescription counts. It shows how many people in every thousand Austrralians are taking the standard dose of a drug every day. DDD includes use in combination products. The calculation is based on ABS 3101.0 – Australian Demographic Statistics for December 2018.

† DDDs for combination products are accounted for in constituent drugs

‡ The World Health Organization has not allocated a DDD for this drug

Source: Department of Health, December 2019. ©Commonwealth of Australia

BOOK REVIEW

Therapeutic Guidelines: Diabetes.
Version 1

Melbourne: Therapeutic Guidelines Limited; 2019.
271 pages
Also available at www.tg.org.au

This book is of great practical value to the readers of *Australian Prescriber*. It is well-organised – chapters cover the management of the different types of diabetes including type 1 diabetes, type 2 diabetes and diabetes in pregnancy. Each chapter is comprehensive, clear and current. Both non-pharmacological and pharmacological treatments are discussed in depth. The guideline also covers important considerations in the management of diabetes such as driving and pre-conception counselling.

Bolding and underlining of major points help to highlight key aspects of diabetes management. There are also useful tables and figures summarising the information. Evidence is constantly emerging on drugs used for the management of type 2 diabetes, including cardiovascular and renal effects. Future editions of this book will no doubt incorporate ongoing research findings.

I noticed there are some differences in the book compared to other guidelines. In Table 17 'Suggested subcutaneous insulin management on the day of a procedure for adults with type 2 diabetes', for patients with morning basal insulin only or multiple daily injections (basal-bolus) or intermediate-acting insulin twice-daily with rapid- or short-acting insulin bolus who are undergoing an afternoon procedure, the recommendation is to give the patient's usual morning dose of basal insulin. There is a footnote regarding adjustment of insulin dose in a patient whose diabetes is tightly controlled. The Australian Diabetes Society Peri-Operative Diabetes Management Guidelines (2012) suggest halving the patient's morning basal insulin. Given variations in practice, it might be preferable to suggest giving 50–100% of the patient's morning basal insulin dose depending on factors including the patient's glycaemic control.

In the section on 'Management of diabetic retinopathy', dosing information of fenofibrate in renal impairment (eGFR <30 mL/min) is different from the current product information for fenofibrate, which states it is contraindicated when eGFR is less than 30 mL/minute.

In summary, this is a very useful book to a variety of health professionals including GPs, medical specialists, hospital doctors, diabetes educators and pharmacists.

Tamara Milder
PhD candidate, St Vincent's Hospital, Sydney
Garvan Institute of Medical Research, Sydney

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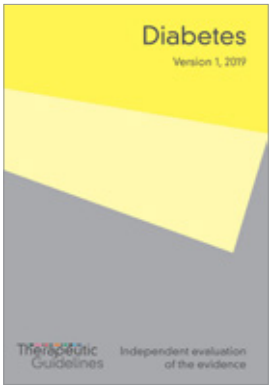

BOOK REVIEW

Therapeutic Guidelines: Ulcers and wound management. Version 2

Kanthi Vemuri
Infectious diseases advanced trainee, Sunshine Coast University Hospital, Queensland

Aust Prescr 2019;206
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Melbourne: Therapeutic Guidelines Limited; 2019. 155 pages
Also available at www.tg.org.au

This latest edition is a brilliant, informative guide to managing ulcers and wounds. It provides a succinct summary and a practical, easy-to-follow framework for managing these challenging conditions. The tables, boxes, figures and illustrative photos help to easily navigate through the important facts, in a timely fashion.

I think the best aspect of this book is that it highlights the importance of early establishment of an aetiology of the ulcer in tailoring the management. This edition has a chapter on skin tears which are so common in older people. It provides information on prevention, assessment and how to avoid complications such as infection and conversion into a chronic ulcer. The chapter on wounds in the high-risk foot describes the importance of prevention and the need to focus on revascularisation and pressure-redistribution strategies during the early assessment.

The emphasis on non-pharmacological measures for ulcer healing such as foot care, foot wear, compression stockings and appropriate dressings highlights the vast experience the expert group has in this field. The well-designed tables provide an excellent guide to choose the appropriate dressings depending on wound characteristics. There is also a new section about a palliative approach to ulcers that are not expected to heal, including pain management and dressing choice.

I highly recommend this latest edition, which incorporates all the known successful strategies, to every clinician involved in ulcer and wound management, both in the hospital and community.

New drugs

Dupilumab

Approved indication: atopic dermatitis

Dupixent (Sanofi-aventis)
Pre-filled syringe containing 300 mg/2 mL solution

Dupilumab is a subcutaneously injected monoclonal antibody for people with moderate–severe atopic dermatitis who require systemic therapy. It is intended for long-term rather than episodic use and can be given with or without topical corticosteroids. Currently, oral immunosuppressants such as ciclosporin, azathioprine or methotrexate are used in severe atopic dermatitis.

People with atopic dermatitis produce increased amounts of interleukin-4 and interleukin-13. Dupilumab inhibits signalling mediated by these cytokines by blocking their receptors.

The safety and efficacy of dupilumab has been investigated in three main placebo-controlled phase III trials. SOLO-1 and SOLO-2 assessed dupilumab monotherapy for 16 weeks and LIBERTY AD CHRONOS assessed dupilumab with concomitant topical corticosteroids for 52 weeks.[1,2] Efficacy in all three trials was measured at 16 weeks.

In total, 2119 people with moderate–severe atopic dermatitis (minimum of 10% body surface area involvement) were enrolled in the three trials. All patients used emollient twice a day. Patients were randomised to one of three treatments:

- an initial loading dose of dupilumab 600 mg subcutaneously as two injections, followed by a 300 mg dose every two weeks
- initial 600 mg dupilumab dose, followed by 300 mg each week
- matching placebo.

A primary outcome of the trials was the proportion of patients with an Investigator's Global Assessment (IGA) score of 0 or 1 (clear or almost clear skin) and a reduction of at least 2 points in their IGA score from baseline, after 16 weeks of treatment.

At baseline, 46–50% of patients had an IGA score of 4. After 16 weeks of treatment, 36–38% of people given dupilumab in the SOLO trials and 39% in the LIBERTY AD CHRONOS trial had reached the primary outcome. This was compared to 8–12% in the corresponding placebo groups (see Table). More improvement of pruritus was also reported with dupilumab compared to placebo.[1,2] Efficacy was maintained at 52 weeks in the LIBERTY AD CHRONOS trial.[2]

The most common adverse events with dupilumab included injection-site reactions (9.6–15.9%), allergic conjunctivitis (3–7%), bacterial conjunctivitis (0.9–1.9%), blepharitis (0.4–4.5%), oral herpes (2.5–3.8%), eye pruritus (0.4–2.9%) and dry eye (0.2–1.8%). These were less common in the placebo groups. In the LIBERTY AD CHRONOS trial, keratitis

Table **Efficacy of dupilumab in moderate–severe atopic dermatitis**

Trial (treatment duration)	Response to treatment after 16 weeks*		
	Placebo	Dupilumab 300 mg fortnightly	Dupilumab 300 mg weekly
SOLO-1 (16 weeks)	10% (23/2224)	38% (85/224)	37% (83/223)
SOLO-2 (16 weeks)	8% (20/236)	36% (84/233)	36% (87/239)
LIBERTY AD CHRONOS (52 weeks)†	12% (39/315)	39% (41/106)	39% (125/319)

* Efficacy defined as the proportion of patients with an Investigator's Global Assessment (IGA) score of 0 or 1 (clear or almost clear skin) and a reduction of at least 2 points in their IGA score from baseline following 16 weeks of treatment.

† Patients received concomitant topical corticosteroids in the LIBERTY AD CHRONOS trial but not in the SOLO trials.

Source: references 1–2

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First published 10 October 2019

Some of the views expressed in the following notes on newly approved products should be regarded as preliminary, as there may be limited published data at the time of publication, and little experience in Australia of their safety or efficacy. However, the Editorial Executive Committee believes that comments made in good faith at an early stage may still be of value. Before new drugs are prescribed, the Committee believes it is important that more detailed information is obtained from the manufacturer's approved product information, a drug information centre or some other appropriate source.

NEW DRUGS

occurred in 4% of patients treated with dupilumab and topical corticosteroid compared to none of the patients treated with placebo and topical corticosteroid. There were occasional elevations in eosinophils with dupilumab but these were usually transient. There were two cases of serum sickness in people with high titres of anti-drug antibody.

There are no data on dupilumab in pregnancy. However, studies in animals did not indicate toxicity. As dupilumab is an IgG antibody, it is expected to cross the placenta and also be excreted in human breast milk.

In theory, dupilumab could affect the immune response to helminth infections. Pre-existing infections should be treated before dupilumab is started. If a patient develops an infection during therapy and does not respond to anti-helminth treatment, dupilumab should be stopped.

It is not known if live vaccines are safe to use in people receiving dupilumab. There are also no data on the concomitant use of other medicines that modulate the immune system.

An initial loading dose of dupilumab 600 mg is recommended, given subcutaneously as two 300 mg injections at different sites. This is followed by a 300 mg dose given every two weeks. Maximum serum concentrations are reached within 3–7 days of injection.

In the trials, 36–39% of patients with moderate to severe dermatitis had clear or almost clear skin after 16 weeks of dupilumab treatment. There appeared to be little extra benefit of adding topical corticosteroids to dupilumab treatment. Injection-site reactions were very common with dupilumab. It is not known how dupilumab will compare to other treatments for severe disease as there were no active comparators in the trials. This drug is not currently approved for children but trials are ongoing. Dupilumab is also being investigated in asthma.

T T manufacturer provided additional useful information

REFERENCES

1. Simpson EL, Bieber T, Guttman-Yassky E, Beck LA, Blauvelt A, Cork MJ, et al.; SOLO 1 and SOLO 2 Investigators. Two phase 3 trials of dupilumab versus placebo in atopic dermatitis. N Engl J Med 2016;375:2335-48.https://doi.org/10.1056/NEJMoa1610020
2. Blauvelt A, de Bruin-Weller M, Gooderham M, Cather JC, Weisman J, Pariser D, et al. Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1-year, randomised, double-blinded, placebo-controlled, phase 3 trial. Lancet 2017;389:2287-303. https://doi.org/10.1016/S0140-6736(17)31191-1

The Transparency Score is explained in New drugs: transparency, Vol 37 No 1, Aust Prescr 2014;37:27.

At the time the comment was prepared, information about this drug was available on the websites of the Food and Drug Administration in the USA, the European Medicines Agency and the Therapeutic Goods Administration.

Neratinib

Aust Prescr 2019;42:209–10
https://doi.org/10.18773/austprescr.2019.074
First published 21 November 2019

Approved indication: breast cancer

Nerlynx (Specialised Therapeutics)
40 mg film-coated tablets

Neratinib is indicated for extended adjuvant treatment in women with early-stage HER2-positive breast cancer following adjuvant trastuzumab-based chemotherapy. It should be started within a year of finishing trastuzumab. Neratinib is a tyrosine kinase inhibitor. It irreversibly binds to the HER1, HER2 and HER4 receptors. This binding reduces auto-phosphorylation and downstream signalling from these receptors and decreases growth of the cells.

The approval of neratinib is based on a placebo-controlled phase III trial of 2840 women who had stage I–III HER2-positive breast cancer.[1,2] Most participants had completed their last trastuzumab dose within a year of starting the trial. Women were randomised 1:1 to receive neratinib (240 mg/day) or placebo for 12 months. The primary outcome of the trial was invasive disease-free survival, which included invasive ipsilateral tumour recurrence, invasive contralateral breast cancer, local or regional recurrence, distant recurrence or death from any cause.

In two-year and five-year analyses, invasive disease-free survival rates were statistically higher with neratinib than with placebo (93.9% vs 91.6% at 2 years and 90.2% vs 87.7% at 5 years). However, there was no statistically significant difference between the neratinib and placebo groups for other outcomes including distant disease-free survival and CNS recurrence (see Table).[1,2] In a subgroup analysis of invasive disease-free survival at five years, women who had completed their last trastuzumab dose more than 12 months before starting the trial gained no benefit from neratinib (hazard ratio=1).[2]

The most common adverse events with neratinib included diarrhoea (93.6%), nausea (42.5%), fatigue (27.3%), vomiting (26.8%), abdominal pain (22.7%), rash (15.4%), decreased appetite (13.7%), stomatitis (11.2%) and muscle spasm (10%). Diarrhoea was severe (grade 3) in 40% of cases,[1] and 14.4% of women discontinued because of it. Loperamide prophylaxis (along with adequate hydration) is therefore recommended for the first 1–2 months of treatment, and as needed after that. The neratinib dose may need to be reduced, interrupted or discontinued depending on the severity of the diarrhoea.

Women with renal impairment have a higher risk of complications from dehydration with diarrhoea and should be closely monitored. Neratinib is not recommended in severe renal impairment or dialysis.

Liver toxicity was more common with neratinib than with placebo (12.4% vs 6.6%) and included elevated alanine aminotransferase, aspartate aminotransferase and blood alkaline phosphatase. The dose may need to be reduced or discontinued depending on the severity of the hepatotoxicity. Neratinib is contraindicated in severe hepatic impairment (Child-Pugh C).

The recommended dose of neratinib is 240 mg once daily for a year. Tablets should be taken in the morning with food. Following oral administration, peak plasma concentrations are reached after seven hours. Neratinib is extensively metabolised in the liver, primarily by cytochrome P450 (CYP) 3A4. Its plasma half-life is 17 hours and most of the dose is excreted in the faeces.

Neratinib has numerous drug interactions. Concomitant use of strong CYP3A4 and P-glycoprotein inducers should be avoided (e.g. carbamazepine, phenobarbital,

Table **Efficacy of neratinib (12 months treatment) in HER2-positive breast cancer after trastuzumab**

	Event-free rate	
	2-year analysis[1]	**5-year analysis**[2]
Outcome	**neratinib vs placebo**	**neratinib vs placebo**
Invasive disease-free survival*	93.9% vs 91.6% (p=0.009)	90.2% vs 87.7% (p=0.008)
Disease-free survival including DCIS	93.9% vs 91% (p=0.001)	89.7% vs 86.8% (p=0.004)
Distant disease-free survival	95.1% vs 93.7% (p=0.089)	91.6% vs 89.9% (p=0.065)
CNS recurrence†	0.91% vs 1.25% (p=0.440)	1.3% vs 1.8% (p=0.333)

DCIS ductal carcinoma in situ
* Invasive disease was defined as ipsilateral tumour recurrence, contralateral breast cancer, local or regional recurrence, distant recurrence or death from any cause.
† Reported as cumulative incidence, not event-free rate

phenytoin, rifampicin and St John's wort). CYP3A4 inhibitors (fluconazole, diltiazem, verapamil, erythromycin) should also not be co-administered. If CYP3A4 inducers or inhibitors cannot be avoided, the neratinib dose should be increased or decreased accordingly (see product information).

Neratinib's solubility goes down with increasing pH, so some drugs may affect its bioavailability. Concomitant proton pump inhibitors should be avoided and neratinib should be given separately from H_2-receptor antagonists and antacids.

As there was evidence of fetal toxicity in animal studies, women should use contraception during and for one month after finishing neratinib treatment. It is unclear if the drug reduces the effectiveness of hormone contraceptives so women should add a barrier method. It is not known if neratinib is excreted in breast milk.

Neratinib improved the invasive-free 5-year survival rate of women with HER2-positive breast cancer by 2.5% compared to placebo. Those with hormone-receptor positive breast cancer seemed to have more benefit than those without the receptor. It is currently unclear whether improved invasive-free survival will lead to improved overall survival. The modest benefits of neratinib have to be weighed against the very high likelihood of diarrhoea, which was severe in 40% of women who were treated.

T manufacturer provided the product information

REFERENCES

1. Chan A, Delaloge S, Holmes FA, Moy B, Iwata H, Harvey VJ, et al. Neratinib after trastuzumab-based adjuvant therapy in patients with HER2-positive breast cancer (ExteNET): a multicentre randomised double-blind placebo-controlled phase 3 trial. Lancet Oncol 2016;17:367-77. https://doi.org/10.1016/S1470-2045(15)00551-3
2. Martin M, Holmes FA, Ejlertsen B, Delaloge S, Moy B, Iwata H, et al. Neratinib after trastuzumab-based adjuvant therapy in HER2-positive breast cancer (ExteNET): 5-year analysis of a randomised double-blind placebo-controlled phase 3 trial. Lancet Oncol 2017;18:1688-700. https://doi.org/10.1016/S1470-2045(17)30717-9

The Transparency Score is explained in New drugs: transparency, Vol 37 No 1, Aust Prescr 2014;37:27.

At the time the comment was prepared, information about this drug was available on the websites of the Food and Drug Administration in the USA, and the European Medicines Agency.

Aust Prescr 2019;42:211
https://doi.org/10.18773/austprescr.2019.075

Crisaborole

Approved indication: atopic dermatitis

Staquis (Pfizer)
tubes containing 2.5 mg and 60 mg 2% ointment

When mild to moderate atopic dermatitis does not respond to moisturisers and emollients, low-dose corticosteroids are usually prescribed. Crisaborole 2% ointment is a new treatment for this condition and is approved for patients aged two years and over. It is a phosphodiesterase type 4 inhibitor and, although its mechanism of action is not clear, inhibiting the phosphodiesterase type 4 enzyme is known to suppress the secretion of pro-inflammatory cytokines such as tumour necrosis factor (TNF) alpha.

A thin layer of ointment should be applied to affected skin twice a day. After administration, 25% of the dose is absorbed. Crisaborole is then rapidly metabolised to inactive metabolites which are excreted by the kidneys. Drug interactions with cytochrome P450 enzymes are not expected. Concurrent use with other topical treatments for atopic dermatitis has not been evaluated.

Crisaborole has been investigated in two identical placebo-controlled studies of 1522 participants.[1] Most of them were children. They were evaluated using the Investigator's Static Global Assessment score (severity scale of 1–4). At baseline, 38.5% of patients had mild disease (score of 2) and 61.5% had moderate disease (score of 3). Crisaborole ointment or vehicle alone was applied twice a day for 28 days. The primary end point of the trials was the proportion of patients who had clear (score of 0) or almost clear (score of 1) skin and at least a 2-point improvement in their score from baseline. At the end of the study period, significantly more of the patients who applied active treatment compared to placebo had successfully responded (31–33% vs 18–25% of patients) (see Table).

Crisaborole ointment was well tolerated in the trials. The most common treatment-related adverse effect was burning or stinging at the application site. This affected 4.4% of those in the crisaborole group and 1.2% in the control group.[1] Contact urticaria has been reported with this ointment (<1% of patients). A 48-week, single-arm extension trial of 517 participants assessed the long-term safety of 28-day treatment courses. The most common treatment-related adverse events included worsening or flare of atopic dermatitis (3.1%), and pain (2.3%) and infection (1.2%) at the application site.[2]

Topical crisaborole seemed to be effective as a short-term treatment for mild to moderate atopic dermatitis. However, there have been no comparative trials with topical corticosteroids so far. Longer-term efficacy is yet to be established.

T T manufacturer provided additional useful information

REFERENCES

1. Paller AS, Wynnis LT, Lebwohl MG, Blumenthal RL, Boguniewicz M, Call RS, et al. Efficacy and safety of crisaborole ointment, a novel nonsteroidal phosphodiesterase 4 (PDE4) inhibitor for the topical treatment of atopic dermatitis (AD) in children and adults. J Am Acad Dermatol 2016;75:494-503. https://doi.org/10.1016/j.jaad.2016.05.046
2. Eichenfield LF, Call RS, Forsha DW, Fowler J Jr, Herbert AA, Spellman M, et al. Long-term safety of crisaborole ointment 2% in children and adults with mild to moderate atopic dermatitis. J Am Acad Dermatol 2017;77:641-9. https://doi.org/10.1016/j.jaad.2017.06.010

The Transparency Score is explained in New drugs: transparency, Vol 37 No 1, Aust Prescr 2014;37:27.

At the time the comment was prepared, information about this drug was available on the websites of the Food and Drug Administration in the USA and the Therapeutic Goods Administration.

Table **Efficacy of twice-daily crisaborole 2% ointment for mild–moderate atopic dermatitis**

	Proportion of patients who successfully responded after 28 days of treatment*		
	Crisaborole (1016 patients)	Placebo vehicle (506 patients)	P value
Trial 1	32.8%	25.4%	0.038
Trial 2	31.4%	18%	<0.001

* The primary efficacy end point was the proportion of patients who had clear (score of 0) or almost clear (score of 1) skin evaluated using the Investigator's Static Global Assessment score (severity scale of 1–4), and at least a 2-point improvement in their score from baseline.

Source: reference 1

NEW DRUGS

Update

Antipsychotic switching tool [Update]

Aust Prescr 2019;42:213
https://doi.org/10.18773/austprescr.2019.072
First published 29 October 2019

The online tool by Nicholas Keks et al has been updated. View updated tool.

The risperidone depot switches to aripiprazole and flupentixol have been updated to include recommendations to start at 25% of the target dose if starting within 3 weeks of the last injection of risperidone. All risperidone depot switches, except the switch to paliperidone, include extra clarification for this recommendation.

The source material used for the tool has also been included.

EDITORIAL OFFICE

For general correspondence such as Letters to the Editor, contact the Editor.

Postal The Editor
Australian Prescriber
Level 5, 15 Moore Street
Canberra, ACT 2600

Telephone +61 2 8217 8700

Email info@australianprescriber.com

Website nps.org.au/australian-prescriber

Twitter @AustPrescriber

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